Exhibit C

Listing and copies of references relied upon

PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Protest of Application of:	)	
	)	
Ferenc MARTENYI et al.	)	Group Art Unit: Unknown
	)	
Application No.: 10/550,382 (U.S. National Stage of International Application No. PCT/EP2004/003590)	)	Examiner: Unknown
	)	
International Filing Date: April 1, 2004	)	
	)	
U.S. National Stage entry: September 21, 2005	)	
	)	
For: USE OF 10-HYDROXY-10,11-DIHYDROCARBAMAZEPINE DERIVATIVES FOR THE TREATMENT OF AFFECTIVE DISORDERS	)	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

EXHIBIT C: LISTING AND COPIES OF REFERENCES RELIED UPON IN PROTEST UNDER 37 C.F.R. § 1.291(a)

1) U.S. Patent No. 3,637,661 issued January 25, 1972, to Schindler;

2) U.S. Patent No. 5,753,646 issued May 19, 1998, to Benés et al.;

3) U.S. Patent No. 6,296,873 issued October 2, 2001, to Katzhendler et al.;

4) U.S. Patent Publication No. 2005/0004102 published January 6, 2005, to Schmutz;

5) Ambrósio et al., *Neurotoxic/neuroprotective profile of carbamazepine, oxcarbazepine and two new putative antiepileptic drugs, BIA 2-093 and BIA 2-024*, European Journal of Pharmacology, 406, pp. 191-201 (2000);

6) Baruzzi et al., *Oxcarbazepine: Pharmacokinetic Interactions and Their Clinical Relevance*, Epilepsia, 35 (Suppl. 3), pp. S14-S19 (1994);

7) Dietrich et al., *Oxcarbazepine in Affective and Schizoaffective Disorders*, Pharmacopsychiatry, 34, pp. 242-250 (2001);

8) Gelenberg et al., *Treating Bipolar Disorder: Toward the Third Millennium*, XVIII (4) Psych. Times (electronic version, 7 pages) (2001)

9) Hainzl et al., *Metabolism of two new antiepileptic drugs and their principal metabolites S(+)- and R(-)-10,11-dihydro-10-hydroxy carbamazepine*, Epilepsy Research, 44, pp. 197-206 (2001)

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Neurotoxic/neuroprotective profile of carbamazepine, oxcarbazepine and two new putative antiepileptic drugs, BIA 2-093 and BIA 2-024

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Abstract

We investigated and compared the toxicity profile, as well as possible neuroprotective effects, of some antiepileptic drugs in cultured rat hippocampal neurons. We used two novel carbamazepine derivatives, (*S*)-(−)-10-acetoxy-10,11-dihydro-5*H*-dibenz[*b,f*]azepine-5-carboxamide (BIA 2-093) and 10,11-dihydro-10-hydroxyimino-5*H*-dibenz[*b,f*]azepine-5-carboxamide (BIA 2-024), and compared their effects with the established compounds carbamazepine and oxcarbazepine. The assessment of neuronal injury was made by using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl (MTT) assay, as well as by analysing morphology and nuclear chromatin condensation (propidium iodide staining), after hippocampal neurons were exposed to the drugs for 24 h. The putative antiepileptic drugs, BIA 2-093 or BIA 2-024 (at 300 μM), only slightly decreased MTT reduction, whereas carbamazepine or oxcarbazepine were much more toxic at lower concentrations. Treatment with the antiepileptic drugs caused nuclear chromatin condensation in some neurons, which is characteristic of apoptosis, and increased the activity of caspase-3-like enzymes, mainly in neurons treated with carbamazepine and oxcarbazepine. The toxic effect caused by carbamazepine was not mediated by *N*-methyl-D-aspartate (NMDA) or by α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) receptors. Moreover, the antiepileptic drugs failed to protect hippocampal neurons from the toxicity caused by kainate, veratridine, or ischaemia-like conditions.

Keywords: Antiepileptic drug; Neurotoxicity; Neuroprotection; Apoptosis

1. Introduction

Epilepsy is one of the most common neurological diseases, affecting at least 50 million people worldwide (Scheuer and Pedley, 1990). The major antiepileptic drugs in clinical use, i.e. phenytoin, carbamazepine, valproate and phenobarbital, among others, were developed and introduced between 1910 and 1970, and are referred to as "first-generation" drugs. Several new anticonvulsant drugs, such as vigabatrin, gabapentin, felbamate, lamotrigine and oxcarbazepine, have been introduced into clinical practice and are referred to as "second-generation" drugs. More recent anticonvulsants, which are in preclinical or clinical development, can be considered as "third-generation" drugs (Löscher, 1998a).

Carbamazepine has become the most frequently prescribed first-line drug for the treatment of partial and generalised tonic–clonic epileptic seizures (Loiseau and Duché, 1995). Moreover, carbamazepine has been used in the treatment of neuropathic pain and schizoaffective psychosis. However, patients treated with carbamazepine may develop toxic symptoms, such as drowsiness, dizziness, ataxia and nausea. Other disadvantages of carbamazepine are its enzyme-inducing properties (Tateishi et al., 1999) and interaction with other drugs (Yasui et al., 1997), as well as the increase in the incidence of congenital malformations (Kaneko et al., 1999). Although most of the toxic symptoms of carbamazepine are in the central nervous system (CNS), the mechanisms by which this antiepileptic

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drug causes toxicity are not completely clarified. Some reports indicate that carbamazepine induces apoptosis in cultured cerebellar granule cells (Gao and Chuang, 1992; Nonaka et al., 1998) and decreases glutamine synthetase activity (Fraser et al., 1999). Conversely, it was previously shown that carbamazepine exerted protective effects against focal ischaemia or anoxia (Fern et al., 1993; Rataud et al., 1994; Minato et al., 1997), or against toxicity induced by glutamate or veratridine (Mattson and Kater, 1989; Lakics et al., 1995; Mark et al., 1995). In addition, carbamazepine did not prevent status epilepticus-induced damage to neurons in hippocampus and amygdala (Pitkänen et al., 1996).

Oxcarbazepine is an analogue of carbamazepine, with a comparable anticonvulsant efficacy. It has the advantage of a low incidence of allergic reactions and enzyme induction. In case of combination therapy with other antiepileptic drugs, oxcarbazepine is usually better tolerated than carbamazepine (Elger and Bauer, 1998). However, the involvement of oxcarbazepine in neuronal toxicity has not been investigated.

Since seizures are resistant to treatment with currently available antiepileptic drugs in about 30% of patients with epilepsy, more effective antiepileptic drugs are necessary. In addition, because of the inadequacy of the currently available antiepileptic drugs, in terms of safety, newly developed drugs should be less toxic than existing drugs. (*S*)-(−)-10-acetoxy-10,11-dihydro-5*H*-dibenz[*b,f*]azepine-5-carboxamide (BIA 2-093; Benes et al., 1999a) and 10,11-dihydro-10-hydroxyimino-5*H*-dibenz[*b,f*]azepine-5-carboxamide (BIA 2-024; Benes et al., 1999b) are representative of new compounds, structurally related to carbamazepine and oxcarbazepine, with anticonvulsant activity, as determined by maximal electroshock (Benes et al., 1999a,b). These two compounds were specifically designed to circumvent their further degradation to toxic metabolites, such as epoxides, without losing anticonvulsant potency. For example, BIA 2-093 produces significantly less motor and cognitive impairment than carbamazepine and oxcarbazepine (Benes et al., 1999a). In the present work, we used an in vitro system (cultured hippocampal neurons), to investigate the toxic profile of BIA 2-093 and BIA 2-024, as well as their possible protective effects against several neurotoxic insults, in comparison with the antiepileptic drugs carbamazepine and oxcarbazepine.

2. Materials and methods

2.1. Cell culture

Hippocampal neurons were dissociated from hippocampi of E18–E19 Wistar rat embryos, after treatment with trypsin (1.0 mg/ml; 15 min; 37°C) and deoxyribonuclease I (0.15 mg/ml) in Ca^{2+}- and Mg^{2+}-free Hank's balanced salt solution (137 mM NaCl, 5.36 mM KCl, 0.44 mM KH_2PO_4, 0.34 mM $Na_2HPO_4.2H_2O$, 4.16 mM $NaHCO_3$, 5 mM glucose, supplemented with 0.001% phenol red, 1 mM sodium pyruvate, 10 mM HEPES, pH 7.4). Hippocampal neurons were cultured in B27-supplemented Neurobasal medium (GIBCO), a serum-free medium combination (Brewer et al., 1993), supplemented with glutamate (25 μM), glutamine (0.5 mM) and gentamicin (0.12 mg/ml). Cultures were kept at 37°C in a humidified incubator in 5% CO_2/95% air, for 7–8 days, the time required for maturation of hippocampal neurons.

For the assessment of neuronal injury with the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, or to measure the activity of caspase-3-like enzymes, hippocampal neurons were plated on poly-D-lysine-coated (0.1 mg/ml) multiwells at a density of 0.1×10^6 or 0.2×10^6 cells/cm^2, respectively. For morphology studies with Cresyl violet staining, or analysis of nuclear condensation/fragmentation with propidium iodide staining, cells were plated at a density of 45×10^3 cells/cm^2 on poly-D-lysine-coated coverslips.

2.2. Exposure of hippocampal neurons to drugs

The hippocampal neurons were exposed to drugs for 24 h. The drugs were diluted in aliquots of 250 μl of conditioned medium, taken from each well and placed in an Eppendorf tube. Then, the aliquots were added back to the corresponding well, and the medium was mixed gently to preserve the integrity of neurons. The toxicity was assessed by using either the MTT assay, by analysing neuronal morphology, or by counting neurons with nuclear condensation and/or fragmentation. The activity of caspase-3-like enzymes was also measured, as described in the next.

2.3. MTT assay

Assessment of neuronal injury in cultured hippocampal neurons was made by using the MTT assay. Briefly, Krebs buffer with MTT (0.5 mg/ml) was added to the cultures and incubated for 1 h at 37°C in the incubation chamber. MTT, when taken up by living cells, is converted from a yellow to a water-insoluble blue-coloured product. The precipitated dye was dissolved in 0.04 M HCl in isopropanol and colorimetrically (absorbance at 570 nm) quantitated.

2.4. Morphology studies

After incubation of cultured hippocampal neurons with the drugs, for 24 h, the culture medium was removed, the cells were washed two times with phosphate-buffered saline (PBS; 137 mM NaCl, 2.7 mM KCl, 10 mM Na_2HPO_4, 1.8 mM KH_2PO_4, pH 7.4), and fixed with 0.1% glutaralde-

hyde in PBS at 37°C. After 30 min, the cells were washed two times with PBS (10 min each time) and then dehydrated in a gradient of ethanol/PBS (50%, 70%, 80%, 95% and 100% ethanol) and ethanol/acetone 1:1, about 1 min per solution. After this procedure, the cells were rehydrated in a gradient of ethanol/PBS (100%, 95%, 80%, 70% and 50% ethanol) and then washed two times with PBS. The cells were stained with 0.5% Cresyl violet for 5 min, washed several times with ultrapurified water, and dried. Finally, the coverslips containing the cells were mounted with Entellan (Merck), and micrographs were taken.

2.5. Propidium iodide staining

After incubation with the drugs, cells were fixed in 4% paraformaldehyde and then stained with propidium iodide (1.3 μg/ml) in Krebs medium. Apoptotic neurons, with condensed/fragmented nuclei, were counted by using a fluorescence microscope and a triple filter (Omega Optical XF63). The neuronal counting was done by counting approximately 200 neurons in about 10 fields in each coverslip.

2.6. Caspase-3-like activity assay

After the exposure of hippocampal neurons to drugs for 24 h, the culture medium was aspirated, and the cultures were washed two times with the following buffer: 50 mM KCl, 50 mM PIPES, 10 mM EGTA and 2 mM $MgCl_2$, pH 7.4, at 4°C. The cells were again washed with the washing buffer supplemented with 100 μM phenyl-methyl-sulfonyl-fluoride, 1 mM dithiothreitol and 1 μg/ml Chymostatin-Leupeptin-Antiparin-Pepstatin A (CLAP). After this procedure, cells were lysed at 4°C with the previous supplemented buffer, with 0.5% Triton, collected and frozen/thawed at −80°C (three times). Protein concentration was determined, and 20 μg of protein was used for each determination. The extract (20 μg) was added to 40 μl of reaction buffer (25 mM HEPES, 0.1% 3-[(3-cholamidopropyl)dimethylammonio]-1-propane-sulfonate (CHAPS), 10 mM dithiothreitol, 100 μM phenyl-methyl-sulfonyl-fluoride, pH 7.5, which was supplemented with 100 μM Asp-Glu-Val-Asp-7-amino-4-trifluoromethyl coumarin (DEVD-AFC), a fluorogenic substrate for caspase-3 and related proteases) and incubated for 30 min, at 37°C.

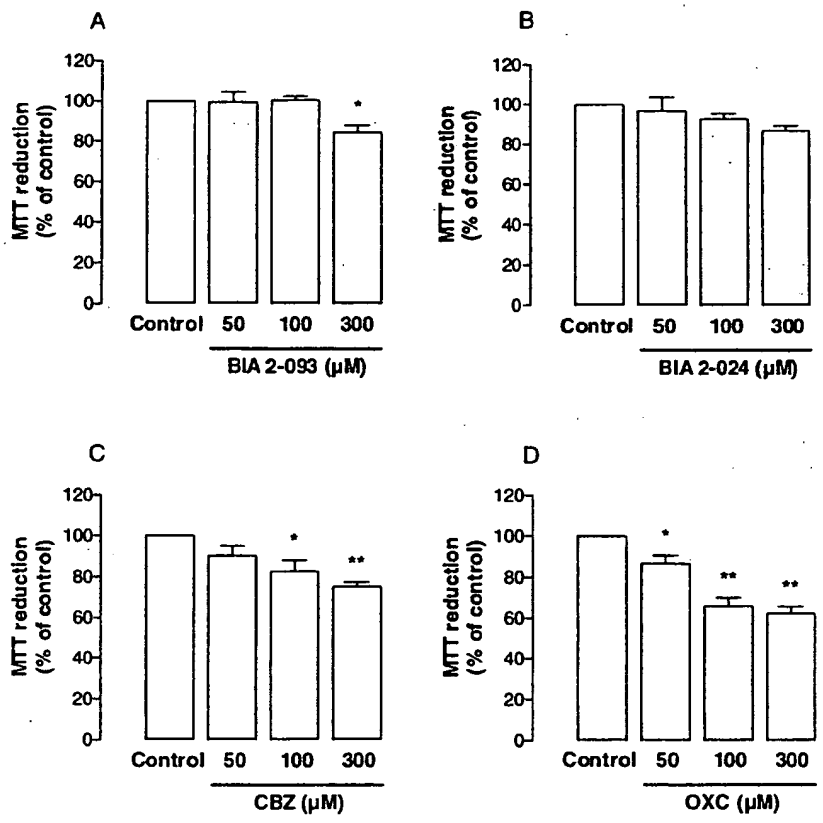

Fig. 1. Neurotoxic effect caused by exposure of cultured hippocampal neurons to antiepileptic drugs for 24 h. (A) BIA 2-093 (B) BIA 2-024 (C) Carbamazepine (CBZ) (D) Oxcarbazepine (OXC). The concentrations of the antiepileptic drugs are indicated below the bars. The results are presented as percentage of MTT reduction, compared to control conditions (no drug), and represent the means ± S.E.M. of at least three independent experiments performed in triplicate. $^{*}P < 0.05$, $^{**}P < 0.01$ — Significantly different from control; Dunnett's post-test.

After incubation, the fluorescence was monitored (excitation from 300 to 410 nm and emission 475 nm) using a Spex Fluoromax spectrofluorometer. The results are expressed as percentage of control (no treatment), using arbitrary fluorescence units, at an excitation wavelength of 390 nm.

2.7. Ischemia-like conditions experiments

Hippocampal neurons were exposed to Krebs medium without glucose and supplemented with 2-deoxyglucose (5 mM) and sodium cyanide (2.5 mM), which inhibits cytochrome *c* oxidase, for 10 min. After this period, neurons were washed two times with Krebs medium with glucose and incubated with Neurobasal medium in an incubation chamber at 37°C, for a 1- or 2-h recovery period. The antiepileptic drugs tested were present during the ischaemic period and during the recovery period. After this period, the metabolic activity was assessed by using the MTT assay.

2.8. Chemicals

BIA 2-093, BIA 2-024, carbamazepine and oxcarbazepine were obtained from BIAL, S. Mamede do Coronado, Portugal. (−)-1-(4-Aminophenyl)-4-methyl-7,8-methylenedioxy-4,5-dihydro-3-methylcarbamoyl-2,3-benzodiazepine (LY 303070) was a kind gift of Lilly Research Laboratories, Indianapolis, IN, USA, and dizocilpine (MK-801) was a kind gift of Merck Sharp and Dohme, NJ, USA. Neurobasal medium, B27 supplement, gentamicin and trypsin (USP grade) were purchased from GIBCO BRL, Life Technologies, Scotland. Glutamate, DNase (DN-25), veratridine, 2-deoxyglucose, sodium cyanide, phenyl-methyl-sulfonyl-fluoride, CLAP and dithiothreitol were purchased from Sigma, St. Louis, MO, USA. Kainate was purchased from TOCRIS, Bristol, UK. Glutaraldehyde and paraformaldehyde were obtained from Merck-Schuchardt, Germany. Propidium iodide was purchased from Molecular Probes, Leiden, The Netherlands. All other reagents were from Sigma or from Merck-Schuchardt.

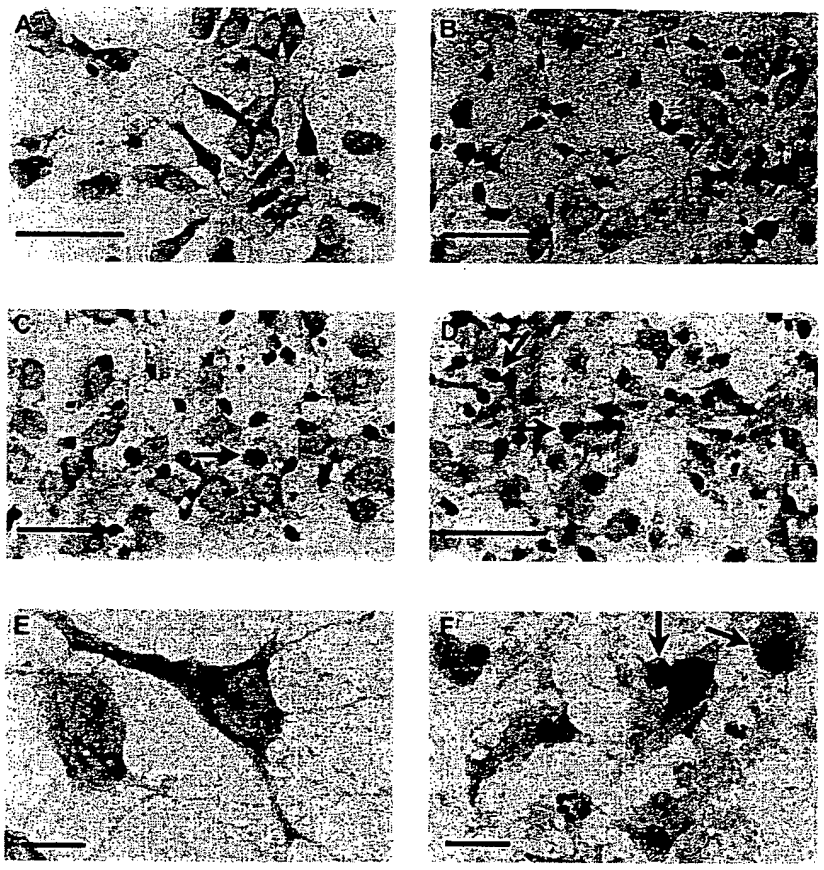

Fig. 2. Changes in the morphology of cultured hippocampal neurons treated with antiepileptic drugs for 24 h. (A) Control culture (B) 300 μM BIA 2-093 (C) 300 μM carbamazepine (D) 300 μM oxcarbazepine — 400× magnification; (E) Control (F) 300 μM oxcarbazepine — 1000× magnification. The morphological aspect of hippocampal neurons treated with BIA 2-024 (not shown) or BIA 2-093 was similar. Micrographs show neurons stained with 0.5% Cresyl violet. The black bar in (A–D) represents 50 μm and in (E–F) represents 10 μm. The arrows show condensed and/or fragmented nuclei.

Carbamazepine, oxcarbazepine, BIA 2-093, BIA 2-024, veratridine and LY 303070 stock solutions were prepared in dimethyl sulfoxide (DMSO).

2.9. Statistical analysis

The data are expressed as means ± S.E.M. Statistical significance was determined by using an analysis of variance (ANOVA), followed by Dunnett's or Bonferroni's post-tests, as indicated in the figure legends.

3. Results

3.1. Effects of antiepileptic drugs on the viability of cultured rat hippocampal neurons

We investigated the effect of 24 h exposure of cultured hippocampal neurons to BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine. The presence of 300 μM BIA 2-093 for 24 h decreased the MTT reduction to 84.4 ± 3.5% ($P < 0.05$), as compared to control (no drug treatment; Fig. 1A). Lower concentrations of BIA 2-093 (50 and 100 μM) did not cause toxicity. In the presence of BIA 2-024 (300 μM) the MTT reduction was 86.8 ± 2.4% of the control ($P > 0.05$; Fig. 1B). Treatment of hippocampal neurons either with carbamazepine or with oxcarbazepine caused a neurotoxic effect at lower concentrations, as compared to BIA 2-093 or BIA 2-024. In the presence of 100 or 300 μM carbamazepine, the MTT reduction decreased to 82.8 ± 5.3% ($P < 0.05$) or 75.4 ± 2.3% ($P < 0.01$) of the control, respectively (Fig. 1C). The toxic effect caused by oxcarbazepine was even higher. Thus,

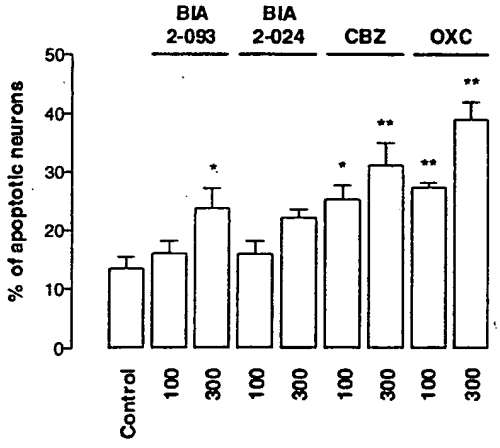

Fig. 3. Quantification of apoptotic hippocampal neurons exposed to antiepileptic drugs for 24 h. The concentration (in μM) of BIA 2-093, BIA 2-024, carbamazepine (CBZ) or oxcarbazepine (OXC) is indicated below the corresponding bars. The results are presented as percentages of apoptotic neurons, and represent the means ± S.E.M. of at least three independent experiments. $^{*}P < 0.05$, $^{**}P < 0.01$ — Significantly different from control; Dunnett's post-test.

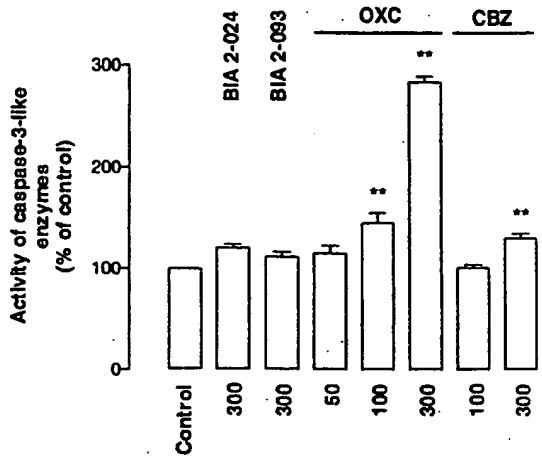

Fig. 4. Activation of caspase-3-like enzymes in cultured hippocampal neurons exposed to antiepileptic drugs. The concentration (in μM) of BIA 2-024, BIA 2-093, oxcarbazepine (OXC) or carbamazepine (CBZ) is indicated below the corresponding bars. The results are presented as percentages of control (no treatment), using arbitrary fluorescence units at an excitation wavelength of 390 nm, and represent the means ± S.E.M. of at least three independent experiments. $^{**}P < 0.01$ — Significantly different from control; Dunnett's post-test.

treatment of hippocampal neurons with 50, 100 or 300 μM oxcarbazepine for 24 h decreased the reduction of MTT to 86.6 ± 3.9% ($P < 0.05$), 65.9 ± 4.2% ($P < 0.01$) or 62.5 ± 3.2% of the control, respectively (Fig. 1D). We also exposed hippocampal neurons to the antiepileptic drugs for shorter periods (1 h) and measured metabolic activity 24 h later, in order to assess possible delayed neurotoxic effects, but the results indicated that the antiepileptic drugs were not toxic under these conditions (not shown).

Morphological studies showed neuronal deterioration, mainly in hippocampal neurons exposed to high concentrations of carbamazepine or oxcarbazepine (Fig. 2). However, some morphological changes were also observed in neurons treated with high concentrations of either BIA 2-093 or BIA 2-024. In Fig. 2, hippocampal neurons treated with BIA 2-024 are not shown since the morphological changes were similar to those of neurons treated with BIA 2-093. Some neurons showed nuclear condensation, indicative of apoptosis, and other neurons appeared to be disintegrated, suggesting necrotic-like cell death.

We also analysed nuclear condensation/fragmentation in cultured hippocampal neurons exposed to the antiepileptic drugs, by using propidium iodide, which stains nucleic acids in cells pre-fixed with paraformaldehyde. In control cultures, 13% of total neurons were apoptotic. In the presence of 100 or 300 μM BIA 2-093, the proportion of apoptotic neurons was 16 ± 2% or 23 ± 3% ($P < 0.05$) of total neurons, respectively (Fig. 3). Similar results were obtained with BIA 2-024: the proportion of apoptotic neurons in cultures treated with 100 or 300 μM BIA 2-024 was 15 ± 2% or 22 ± 1% of total neurons, respectively. The number of apoptotic neurons significantly increased in

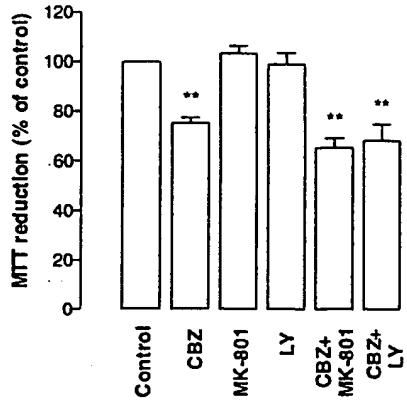

Fig. 5. Lack of protective effect of NMDA or AMPA receptor antagonists on neuronal degeneration caused by carbamazepine (CBZ; 300 μM). NMDA receptor antagonist-MK-801 (10 μM); AMPA receptor antagonist-LY 303070 (LY; 15 μM). The results represent the means ± S.E.M. of at least three independent experiments performed in triplicate, and are presented as percentages of MTT reduction, compared to control conditions (no drug treatment). $^{*}P < 0.05$, $^{**}P < 0.01$ — Significantly different from control; Dunnett's post-test.

the presence of either carbamazepine or oxcarbazepine. Thus, when hippocampal neurons were exposed to 100 or 300 μM carbamazepine the proportion of apoptotic neurons was 25 ± 2% ($P < 0.05$) or 31 ± 3% ($P < 0.01$), respectively. In the case of oxcarbazepine (100 or 300 μM) the proportion of apoptotic neurons was 27 ± 1% ($P < 0.01$) or 39 ± 3% ($P < 0.01$) of total neurons, respectively (Fig. 3). These results indicate that the antiepileptic drugs may cause apoptosis, at least at higher concentrations.

3.2. Effects of antiepileptic drugs on the activity of caspase-3-like enzymes

We measured the activity of caspase-3 and related proteases in hippocampal neurons treated with antiepileptic drugs by using a fluorogenic substrate for these enzymes. The activity of caspase-3-like enzymes was higher in oxcarbazepine-treated neurons than in neurons treated with the other antiepileptic drugs (Fig. 4). The presence of BIA

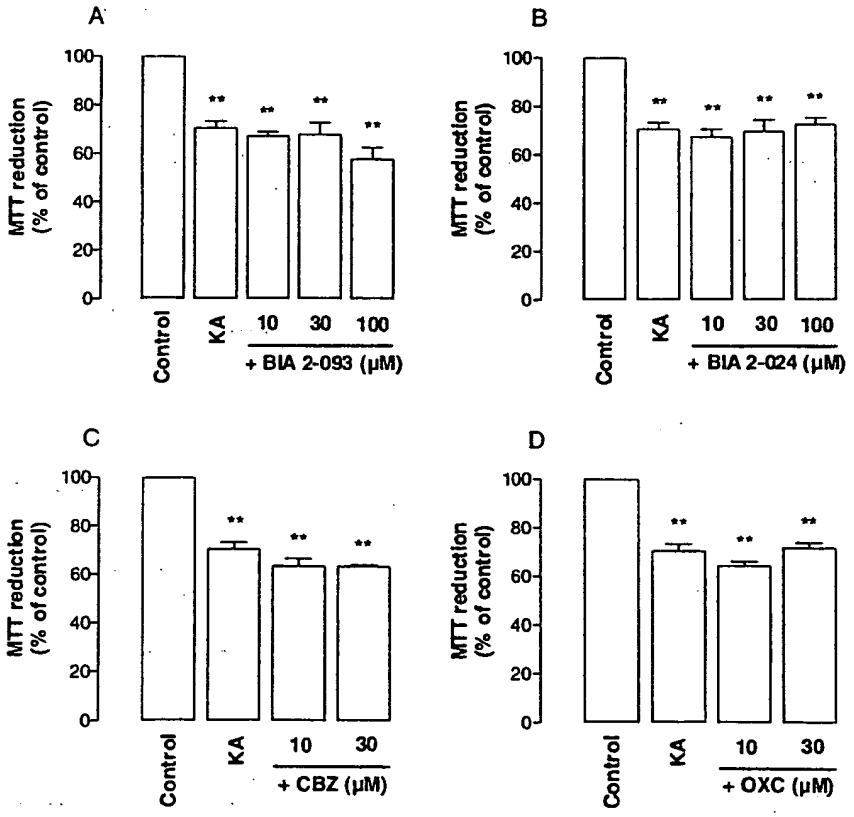

Fig. 6. Lack of protective effect of BIA 2-093, BIA 2-024, carbamazepine (CBZ) or oxcarbazepine (OXC) on neuronal degeneration caused by exposure of hippocampal neurons to kainate (KA; 100 μM) for 24 h. The concentrations of the antiepileptic drugs are indicated below the bars. The results represent the means ± S.E.M. of at least three independent experiments performed in triplicate, and are presented as percentages of MTT reduction under control conditions (no drug treatment). $^{**}P < 0.01$ — Significantly different from control; Dunnett's post-test.

2-024 (300 μM) or BIA 2-093 (300 μM) increased the activity of caspase-3-like enzymes to only 120.7 ± 3.8% ($P > 0.05$) or 112.1 ± 4.8% ($P > 0.05$) of the control, respectively. However, oxcarbazepine and carbamazepine caused a higher and significant increase, especially at high concentrations. Thus, oxcarbazepine (50, 100 and 300 μM) increased the activity of caspase-3-like proteases to 115.4 ± 7.9% ($P > 0.05$), 145.8 ± 9.8% and 283.9 ± 5.6% of the control, respectively. In the case of carbamazepine (300 μM), the activity of caspase-3-like enzymes increased to 130.9 ± 4.7% of the control, and no effect was observed at 100 μM.

3.3. Effects of N-methyl-D-aspartate (NMDA) or α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) receptor antagonists on the toxicity caused by carbamazepine

We also checked whether NMDA or AMPA receptors are involved in the neurotoxic effect caused by carbamazepine. For this purpose, we treated hippocampal neurons with a high concentration of carbamazepine (300 μM) in the presence of either MK-801 (10 μM), a NMDA receptor antagonist, or LY 303070 (15 μM), an AMPA receptor antagonist, and observed that these glutamate receptor antagonists did not protect neurons from the toxicity caused by carbamazepine (Fig. 5). Similar results were obtained in neurons treated with oxcarbazepine (not shown), suggesting that NMDA and AMPA receptors are not involved in the toxicity caused by carbamazepine or oxcarbazepine.

3.4. Kainate-induced neurotoxicity in cultured hippocampal neurons: lack of protection by BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine

Non-NMDA receptor activation contributes to the epileptic phenomena and is also implicated in excitotoxicity. Thus, we investigated whether BIA 2-093, BIA 2-024, carbamazepine and oxcarbazepine act as neuroprotectors against the neurotoxic effect caused by kainate. Treatment of cultured hippocampal neurons with 100 μM kainate for 24 h decreased MTT reduction to 70.5 ± 2.9% of the control (Fig. 6). As previously shown, this neurotoxic effect was mainly due to the activation of AMPA receptors

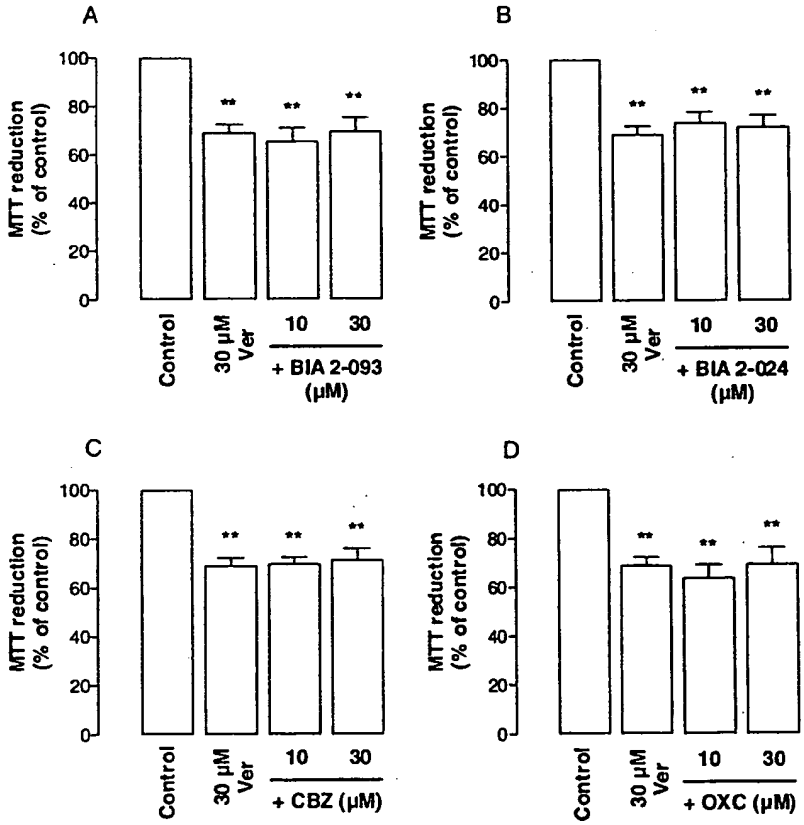

Fig. 7. Lack of protective effect of BIA 2-093, BIA 2-024, carbamazepine (CBZ) or oxcarbazepine (OXC) on neuronal degeneration caused by veratridine (Ver; 30 μM). The results represent the means ± S.E.M. of at least three independent experiments performed in triplicate, and are presented as percentages of MTT reduction under control conditions (no drug). ** $P < 0.01$ — Significantly different from control; Dunnett's post-test.

(Ambrósio et al., 2000). The presence of BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine, at concentrations below those that did not cause any toxic effect, did not protect neurons from kainate-induced toxicity (Fig. 6).

3.5. Veratridine-induced neurotoxicity: lack of protection by BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine

The antiepileptic drugs BIA 2-093 (Benes et al., 1999a), BIA 2-024 (unpublished data), carbamazepine and oxcarbazepine (McLean et al., 1994; Kuo et al., 1997; Benes et al., 1999a) are known to block voltage-sensitive sodium channels. We investigated whether these antiepileptic drugs could protect hippocampal neurons against veratridine-induced toxicity. Veratridine caused a concentration-dependent neurotoxic effect. We observed that in hippocampal neurons treated for 24 h with 10, 30 or 50 μM veratridine the MTT reduction decreased to 85.6 ± 1.8% ($P > 0.05$), 68.9 ± 3.5% ($P < 0.01$) or 49.7 ± 2.3% of the control, respectively. In order to test the efficacy of the antiepileptic drugs in protecting hippocampal neurons, we chose the lowest concentration of veratridine that caused a significant neurotoxic effect: 30 μM. The results obtained show that the antiepileptic drugs, at concentrations below those that caused toxicity, did not protect hippocampal neurons from veratridine-induced toxicity (Fig. 7).

3.6. Chemical ischaemia-induced toxicity: lack of protection by BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine

Some reports indicate that antiepileptic drugs may be neuroprotective under ischaemic conditions (Rataud et al., 1994; Taylor, 1996). We further investigated a possible neuroprotective role of BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine, by testing their effects in hippocampal neurons exposed to ischaemia-like conditions. Exposure of hippocampal neurons to both 5 mM 2-deoxyglucose and 2.5 mM sodium cyanide, for 10 min, decreased the MTT reduction to 49.0 ± 3.7% of the control (Fig. 8A). After washing and a further 1-h incubation in Neurobasal medium, neurons partially recovered their metabolic activity, since the MTT reduction increased to 69.3 ± 4.1% of the control ($^{++}P < 0.01$, as compared to that after a 10-min exposure to deoxyglucose plus cyanide). However, 2 h after exposure to ischaemia-like conditions, an impairment of metabolic activity was observed, since the MTT reduction was similar (54.2 ± 3.3% of the control) to that observed when neurons were treated with deoxyglucose and cyanide for 10 min, without a recovery period. Moreover, when neurons were treated with either deoxyglucose or cyanide, and left to recover for 2 h, the MTT reduction was 83.6 ± 3.6% ($P < 0.05$) or 86.8 ± 4.9% ($P > 0.05$) of the control, respectively (Fig. 8A).

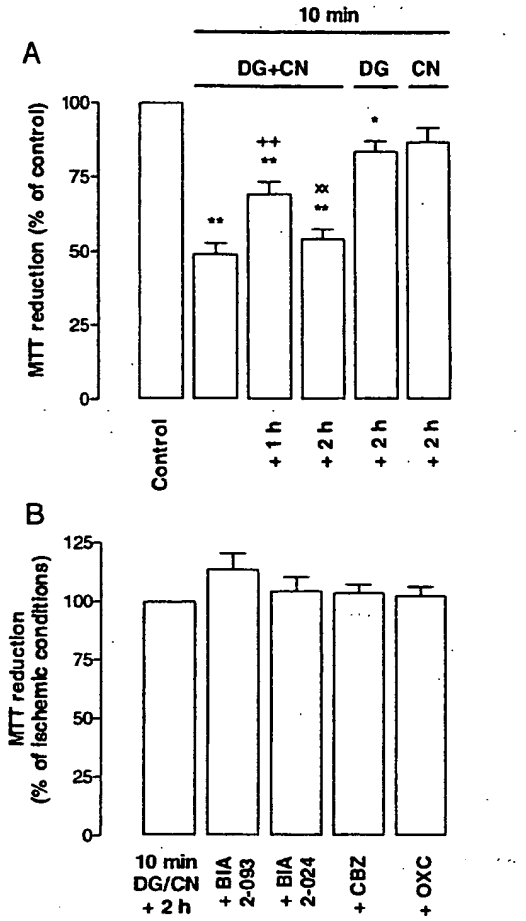

Fig. 8. (A) Evaluation of the metabolic activity of hippocampal neurons exposed to ischaemia-like conditions. Hippocampal neurons were treated with 5 mM 2-deoxyglucose (DG) and/or 2.5 mM sodium cyanide (CN) for 10 min. As indicated below bars, in some cases neurons were left to recover for 1h or 2 h, respectively. The results represent the means ± S.E.M. of at least three independent experiments performed in triplicate, and are presented as percentage of MTT reduction, compared to that under control conditions (no drug). $^{*}P < 0.05$, $^{**}P < 0.01$ — Significantly different from control; Dunnett's post-test. $^{++}P < 0.01$ — Significantly different from chemical-ischaemia conditions; $^{xx}P < 0.01$ — Significantly different from chemical-ischaemia conditions plus 1 h recovery in Neurobasal medium; Bonferroni's post-test. (B) Lack of protective effect of BIA 2-093, BIA 2-024, carbamazepine (CBZ) or oxcarbazepine (OXC) against ischaemia-like conditions in cultured hippocampal neurons. In this particular case, ischaemic conditions were ischaemia-like conditions plus 2 h recovery in Neurobasal medium, in the absence of antiepileptic drugs. In non-control conditions the antiepileptic drugs (300 μM) were present during both ischaemic and recovery periods. The results represent the means ± S.E.M. of at least six independent experiments performed in triplicate, and are presented as percentage of MTT reduction, compared to that under ischaemic conditions.

We then investigated the effect of BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine (at 300 μM) on the metabolic activity of hippocampal neurons exposed to ischaemia-like conditions. The antiepileptic drugs were present when hippocampal neurons were exposed for 10

min to both deoxyglucose and cyanide, as well as during the 2-h recovery period. We chose a concentration of the antiepileptic drugs (300 μM) which was not toxic to hippocampal neurons after a 2-h exposure. The results show that the presence of the antiepileptic drugs did not protect hippocampal neurons from the toxic effect caused by ischaemia-like conditions (Fig. 8B).

4. Discussion

4.1. Neurotoxic effect caused by antiepileptic drugs in cultured hippocampal neurons

It is widely accepted that antiepileptic drugs may cause CNS side effects. For example, antiepileptic drug therapy can affect cognitive function in patients with epilepsy (Delcker et al., 1997; Meador, 1998). Conversely, it has been shown that some antiepileptic drugs have neuroprotective effects (Rataud et al., 1994; Minato et al., 1997). In the present work, we used an in vitro preparation to investigate the neurotoxic/neuroprotective profile of two new anticonvulsants, BIA 2-093 and BIA 2-024, in comparison to the established compounds carbamazepine and oxcarbazepine.

We found that BIA 2-093 and BIA 2-024 were less toxic to hippocampal neurons than are the related compounds, carbamazepine and oxcarbazepine, based on the fact that carbamazepine and oxcarbazepine are more toxic at lower concentrations. Indeed, at the highest concentration used (300 μM), BIA 2-024 did not cause a significant toxic effect, as assessed either by MTT assay or by propidium iodide staining. However, carbamazepine and oxcarbazepine were toxic, although at concentrations above those found in the CSF or plasma. For example, in humans, therapeutic serum levels of carbamazepine are 17–51 μM, and CSF levels may range from 17% to 31% of the plasma concentration (Rogawski and Porter, 1990). Moreover, in rats receiving four times the ED_{50} dose of carbamazepine against maximal electroshock seizure, the peak brain extracellular fluid concentration is approximately 11 μM (Dailey et al., 1997). However, the concentrations used in the present work were not different from the concentrations reported previously (Stefani et al., 1995; Dailey et al., 1997; Nonaka et al., 1998; Benes et al., 1999a; Lingamaneni and Hemmings, 1999). The toxic effect observed at high concentrations may be relevant to some of the adverse syndromes associated with overdosage.

It is important to mention that the antiepileptic drugs studied are not metabolised by neuronal tissue in vitro (unpublished observations), but are rapidly metabolised in vivo, giving origin to various metabolites, some of which are also responsible for the effect of the drugs (Rogawski and Porter, 1990; unpublished observations). Thus, it is difficult to extrapolate these results to an in vivo situation. However, these results may be useful to better understand the mechanism of action of antiepileptic drugs, or even to compare their neurotoxic/neuroprotective profile, since it is important to find new antiepileptic drugs with fewer CNS adverse effects.

Exposure of hippocampal neurons to high concentrations of the antiepileptic drugs caused apoptosis, mainly in the case of oxcarbazepine and carbamazepine, and the apoptotic pathway may involve the activation of caspase-3-like enzymes. It was previously shown that exposure of cultured cerebellar granule cells to carbamazepine for 3 days induced apoptosis (Gao and Chuang, 1992; Gao et al., 1995; Nonaka et al., 1998). Some antiepileptic drugs, including carbamazepine, were found to reduce glutamine synthetase activity in mouse brain (Fraser et al., 1999), and acute CNS side effects in healthy volunteers were also reported (Noachtar et al., 1998). Oxcarbazepine is a new antiepileptic drug that is almost clinically indistinguishable from carbamazepine, but which has some improved properties, as for example in terms of liver enzyme-inducing effects (Elger and Bauer, 1998). To our knowledge, there are no reports in the literature concerning toxic effects of this carbamazepine derivative in the CNS. Surprisingly, we observed that oxcarbazepine was more toxic than carbamazepine. The toxic effect of oxcarbazepine was more pronounced and was observed at lower concentrations.

It is well established that excessive activation of ionotropic glutamate receptors causes neurodegeneration. However, NMDA or AMPA receptors were not involved in the neurotoxic effect caused by high concentrations of carbamazepine, since the toxic effect was not prevented by NMDA or AMPA receptor antagonists.

BIA 2-093 was found to be as potent as carbamazepine, and more potent than oxcarbazepine, in preventing maximal electroshock-induced seizures, when the compounds were given by gastric tube. Both BIA 2-093, carbamazepine and oxcarbazepine caused a dose-dependent motor impairment in rats. When the compounds were given by intraperitoneal route, the protective index for BIA 2-093 was greater than the protective index for carbamazepine and oxcarbazepine (Benes et al., 1999a). Thus, these results, together with our findings, suggest that BIA 2-093 or BIA 2-024 may have some advantages as compared to carbamazepine or oxcarbazepine.

4.2. Toxicity induced by kainate, veratridine or ischaemia-like conditions: lack of protection by BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine

Glutamate is involved in the initiation of seizures and their propagation, and some evidence indicates potential roles for both NMDA and non-NMDA receptors (Löscher, 1998b). Moreover, kainic acid seizure models are widely used to evaluate the efficacy of antiepileptic agents. Taking this into account, we investigated whether BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine, at concentra-

tions that did not cause toxicity, could have a neuroprotective effect on kainate-induced toxicity in hippocampal neurons, which is essentially mediated by the activation of AMPA receptors (Ambrósio et al., 2000). The results show that the antiepileptic drugs did not protect hippocampal neurons from the toxicity caused by kainate.

Contrary to our results, it was previously reported that carbamazepine afforded significant protection against glutamate neurotoxicity in hippocampal cell cultures (Mattson and Kater, 1989; Mark et al., 1995), and reduced NMDA-mediated brain injury (McDonald and Johnston, 1990). It was suggested that the neuroprotective mechanism involved stabilisation of $[Ca^{2+}]_i$. These findings point to beneficial effects of antiepileptic drugs against ionotropic glutamate receptor-mediated injury; however, in our system, the antiepileptic drugs failed to protect hippocampal neurons against toxicity mediated by glutamate receptors. We found previously that carbamazepine inhibited kainate-induced $[Ca^{2+}]_i$ elevation (Ambrósio et al., 1999), but probably this effect was not enough to rescue neurons from kainate-induced toxicity. We also found that ionotropic glutamate receptors, both NMDA and non-NMDA, were not affected by carbamazepine (Ambrósio et al., 1999). Moreover, Grant et al. (1992) showed that the inhibition caused by carbamazepine of NMDA-induced responses appeared to be independent of the NMDA recognition site. These findings suggest that blockade of ionotropic glutamate receptors is not the mechanism by which carbamazepine exerted protective effects in other systems.

Since BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine inhibit voltage-sensitive sodium channels (McLean et al., 1994; Kuo et al., 1997; Benes et al., 1999a; unpublished observations), we investigated whether these antiepileptic drugs could be neuroprotective against veratridine-induced toxicity. The results showed that the antiepileptic drugs did not protect hippocampal neurons from veratridine-induced toxicity. Probably, the concentrations of the antiepileptic drugs were not high enough to inhibit the effect of veratridine. However, it was previously reported that some antiepileptic drugs, including carbamazepine, protected rat cortical cultures against 100 μM veratridine-induced cell death (Lakics et al., 1995). In addition, these authors suggested that mechanisms other than sodium channel blockade may be involved in the neuroprotection.

There is now substantial evidence from animal models that sodium channel blockers prevent neuronal damage caused by global and focal brain ischaemia (Taylor, 1996). We used an ischaemic-like insult (chemical ischaemia) in order to evaluate whether BIA 2-093, BIA 2-024, carbamazepine or oxcarbazepine has a neuroprotective effect in hippocampal neurons. The effect of 2-deoxyglucose and cyanide was synergistic, because exposure of hippocampal neurons to either deoxyglucose or cyanide alone caused only a small toxic effect. The presence of the antiepileptic drugs, during and after the ischaemia-like insult, did not protect hippocampal neurons. Conversely, in vivo studies have demonstrated that some antiepileptic drugs, including carbamazepine, reduce cerebral damage after focal ischaemia in rodents (Rataud et al., 1994; Minato et al., 1997), pointing to a therapeutic potential for voltage-dependent sodium channel blockers. Such compounds may act at sodium channels to prevent depolarisation, inhibiting the release of neurotransmitters such as glutamate and thus protecting the brain. Minato et al. (1997) also showed that carbamazepine ameliorated the effects of brain infarction and improved neurological deficits, but only above the anticonvulsant dose. Contrary to this observation, it was also shown that carbamazepine protected the rat optic nerve against anoxic injury at concentrations well below those used clinically to treat epilepsy (Fern et al., 1993).

Taken together, our results showed that the antiepileptic drugs tested may be toxic to cultured hippocampal neurons, at least at high concentrations, and that the toxic effect is also observed as apoptosis. However, the new putative antiepileptic drugs, BIA 2-093 and BIA 2-024, were less toxic than carbamazepine or oxcarbazepine, with oxcarbazepine being the most toxic. The activation of NMDA or AMPA receptors did not contribute to the toxic effect caused by carbamazepine. In addition, these antiepileptic drugs failed to protect hippocampal neurons against different toxic insults: kainate or veratridine exposure, and ischaemia-like conditions. However, previous findings for other systems, indicate that antiepileptic drugs, under some conditions, can be neuroprotective.

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Oxcarbazepine: Pharmacokinetic Interactions and Their Clinical Relevance

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Summary: Antiepileptic drug (AED) interactions are a common problem during epilepsy treatment. Oxcarbazepine (OCBZ) is a keto homologue of carbamazepine (CBZ) with a completely different metabolic profile. In humans, the keto group is rapidly and quantitatively reduced to form a monohydroxy derivative (MHD), which is the main active agent during OCBZ therapy. MHD is eliminated by renal excretion, glucuronidation and, marginally, by hydroxylation to a diol derivative. This metabolic profile, and in particular the limited involvement of oxidative microsomal enzymes, suggests that OCBZ may have fewer drug interactions compared with traditional AEDs. This possibility has been investigated in experimental studies and, retrospectively, in data obtained from clinical trials. The capacity of OCBZ to induce microsomal enzymes of the P-450 family has mostly been examined by use of antipyrine and CBZ kinetics as markers. The results suggest that OCBZ has little enzyme inducing capacity. In clinical trials in which OCBZ was substituted for CBZ, plasma concentrations of concomitant AEDs were increased, possibly as a consequence of total or partial de-induction. OCBZ interference with other drugs has been evaluated for warfarin, felodipine, and oral contraceptives, three medications strongly influenced by enzyme-inducing AEDs. OCBZ does not modify the anticoagulant effect of warfarin, whereas some reduction in felodipine concentration and a clinically significant reduction of contraceptive drug levels and efficacy were observed. Polytherapy with established AEDs does not significantly modify OCBZ disposition (MHD kinetics); however, available information is not extensive. Finally, the action on OCBZ kinetics of a group of drugs (verapamil, cimetidine, erythromycin, dextropropoxyphene, and viloxazine) known to inhibit the metabolism of some AEDs has been studied. None of the drugs caused kinetic modifications likely to be of clinical relevance. OCBZ has a favorable metabolic profile and fewer drug interactions compared with established AEDs. These findings should be confirmed by more clinical trials and use. **Key Words:** Anticonvulsants—Drug interactions—Oxcarbazepine—Antiepileptic drugs—Drug metabolism—Pharmacokinetics—Drug toxicity.

Antiepileptic drug (AED) interactions are common and represent a frequent clinical problem (Perucca and Richens, 1984; Kutt, 1989). The majority of these interactions involve modifications of the pharmacokinetic parameters. Interactions involving pharmacodynamic parameters may also take place but seem to be rare and, in any case, are much less well documented. Pharmacokinetic interactions can occur at different stages of drug disposition: absorption, distribution, metabolism, and elimination. The propensity of AEDs to drug interactions depends mainly on their metabolic characteristics. Indeed, most AEDs are metabolized in humans by mixed-function oxidases of the cytochrome P-450 family in the liver cells. This system is easily induced and inhibited by several xenobiotics (compounds foreign to the body), including the AEDs (Table 1).

Clearly, all AEDs are prone to one or more kinds of metabolic interactions. Carbamazepine (CBZ), for example, can stimulate its own (autoinduction) or other drugs' metabolism (heteroinduction) and, in turn, its metabolism can be both induced or inhibited by other drugs (Ketter et al., 1991*a*,*b*). Enzyme induction requires some time, as new proteins must be synthesized, and its effect can be observed only after some delay. For example, CBZ metabolic autoinduction requires 2–4 weeks to develop fully. Interactions involving enzyme inhibition usually occur rapidly through two main mechanisms: direct competition for reversible binding sites and irreversible enzyme–drug binding with formation of an inactivated complex. In vivo results may not necessarily reflect in vitro results, and the true net clinical effect can only be determined by studying patients receiving chronic therapy.

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TABLE 1. *Pharmacokinetic interactions of major antiepileptic drugs (AEDs)*

Drug	Possible influence on AED plasma level by		Influence of AED on plasma level of other drug	
	Inducing drug	Inhibiting drug	Reduction	Increase
Phenytoin	Yes	Yes	Yes	Yes
Phenobarbital	Yes	Yes	Yes	No
Primidone	Yes	Yes	Yes	No
Carbamazepine	Yes	Yes	Yes	Yes
Valproate	Yes	No	Yes	Yes
Ethosuximide	Yes	Yes	No	No

KINETIC AND METABOLIC CHARACTERISTICS OF OXCARBAZEPINE

Oxcarbazepine (OCBZ) (Ciba, Basle, Switzerland) is chemically related to CBZ, but the presence of a keto group is sufficient to impart to it a completely different metabolic profile. After oral administration of OCBZ in humans, the keto group undergoes enzymatic reduction to form its active metabolite, the monohydroxy derivative (MHD). Reduction is rapid and almost quantitative, and only minimal amounts of the parent drug are found in peripheral blood (Faigle and Menge, 1990). The MHD metabolite must therefore be considered the main active substance.

The enzymes involved in the reduction of ketones in humans are reported to be noninducible (Faigle and Menge, 1990); as the transformation of OCBZ to MHD is already quantitative, this leaves little room for further metabolic stimulation. Reductase inhibition is theoretically possible, but the potential therapeutic consequences would probably be minimized by the fact that MHD levels should fall as OCBZ concentration rises.

Elimination of MHD occurs through direct renal excretion, glucuronidation and, marginally, hydroxylation to a dihydroxy derivative (DHD) (Faigle and Menge, 1990). Glucuronidation is carried out in humans by a family of UDP-glucuronosyl transferases (UDPGT), which are in general less sensitive to induction or inhibition than microsomal mixed oxidases. However, the list of compounds whose glucuronidation is modified by concomitant drug administration is long and includes compounds such as valproate (VPA), lamotrigine, salicylic acid, and oxazepam (Miners and Mackenzie, 1991). For OCBZ, renal excretion of parent drug and the active metabolite MHD in glucuroconjugated form represents 50% of the oral dose (Feldmann et al., 1981; Theisohn and Heimann, 1982). Only the transformation of MHD to DHD depends on microsomal cytochrome P-450 enzymes; therefore, its minor contribution to OCBZ metabolism practically rules out any important therapeutic interactions.

The fact that OCBZ metabolism depends only marginally on cytochrome P-450 enzymes suggests that OCBZ should not induce this enzymatic system. As described above, enzyme induction is an important source of drug interactions, and a noninducing AED would clearly simplify multiple drug treatments. The enzyme-inducing capacity of OCBZ has been the subject of several investigations. In one study (Larkin et al., 1991), acute (300 mg) and short-term (300 mg twice daily for 2 weeks) OCBZ administration did not significantly modify the kinetics of MHD and antipyrine, the urinary excretion of 6-β-hydroxycortisol or the concentration of circulating androgens. In comparison, similar treatment with CBZ significantly reduced antipyrine half-life (Connell et al., 1984).

Data obtained in patients in whom CBZ treatment was substituted by OCBZ are more controversial. Hulsman et al. (1987) found that, after 3 months of OCBZ therapy, half-lives of antipyrine and CBZ were significantly higher than values during CBZ therapy, suggesting total or partial enzymatic de-induction. With the same study design, however, van Emde Boas et al. (1989) found that the half-life of antipyrine was unchanged and that of CBZ only minimally increased, concluding that OCBZ may possess some specific enzyme-inducing properties. Finally, Patsalos et al. (1990) switched four patients from CBZ to OCBZ and reported a substantial increase in antipyrine half-life in three of these. In the fourth patient, who was receiving the highest OCBZ dosage, antipyrine half-life was unchanged. The authors speculated that OCBZ may have an enzyme-inducing capacity that becomes evident only at high dosages. This possibility, however, has yet to be demonstrated.

Another common source of pharmacokinetic interactions for AEDs is at the level of competitive plasma protein binding (Perucca and Richens, 1984). These interactions, however, are seldom clinically relevant (MacKichan, 1989), and in the case of OCBZ are unlikely to occur because the main active substance (MHD) is only about 40% plasma protein bound (Klitgaard and Kristensen, 1986). Overall, the kinetic and metabolic characteristics suggest that OCBZ treatment should have only limited potential for pharmacokinetic interactions.

EFFECTS OF OCBZ ON AEDs

OCBZ is expected to have little or no effect on the kinetics of other AEDs, but the results of formal studies are not yet available. Some practical information, however, can be obtained from AED plasma concentrations from two polytherapy clinical studies. Houtkooper et al. (1987) reported that the substitution of

OCBZ for CBZ given in association with VPA and/or phenytoin (PHT), at constant dosages, increased VPA and PHT plasma concentrations by 20–30%. Similar data were reported by Battino et al. (1992) on total and free VPA concentrations in young epileptic patients. In both studies, some patients experienced clinical toxicity during OCBZ therapy, possibly because of increased levels of associated drugs. Therefore, when OCBZ is substituted for an inducing drug in polytherapy, the clinical status of the patient and the plasma concentrations of other AEDs should be closely monitored.

EFFECTS OF OCBZ ON OTHER DRUGS

The interaction of AEDs with oral anticoagulants is clinically important (Perucca and Richens, 1984), and the influence of OCBZ on the steady-state anticoagulant effect of warfarin has been investigated by Kramer et al. (1992). A dose of 900 mg administered daily for a week to 10 healthy volunteers, after a warfarin titrating period of 3 weeks, did not significantly modify warfarin action, as measured by prothrombin time (mean Quick values 36.6% at baseline, 38.1% after OCBZ). The authors concluded that when coadministration of warfarin is required, OCBZ offers a clinical advantage over other AEDs, such as phenobarbital (PB), CBZ, and PHT.

The clinical significance of AED interaction with oral contraceptives is well known (Ramsay and Slater, 1991), and the potential effects of OCBZ have been investigated by Klosterskov Jensen et al. (1992). OCBZ 900 mg/day added for a month to a stable oral contraceptive regimen reduced the bioavailability of ethynylestradiol (−48%) and levonorgestrel (−32%). It has been speculated that OCBZ selectively induces specific isozymes of the cytochrome P-450 IIIA group, responsible for the major ethynylestradiol metabolic pathway (Goldzieher, 1990); the same possibility was suggested for levonorgestrel. The incidence of breakthrough bleeding (15%) was considerably higher than that observed when the same oral contraceptives were used without associated drugs.

Similarly, of six women receiving OCBZ in combination with an oral contraceptive containing 30 μg of ethynylestradiol, four (67%) had breakthrough bleeding with OCBZ. In 59 patients treated with CBZ, 37 (63%) had the same adverse effect (Sonnen, 1990). Breakthrough bleeding is a clinical consequence of reduced hormone bioavailability and indicates a diminished contraceptive efficacy. Therefore, the same cautious considerations made with enzyme-inducing AEDs should be applied to OCBZ.

Felodipine, a calcium antagonist, undergoes extensive first-pass oxidative hepatic metabolism and normally has an oral absolute bioavailability of 15%. Drugs such as CBZ, PHT, and PB reduce this bioavailability to less than 1% (Capewell et al., 1988). Because OCBZ metabolism is mainly nonoxidative, no such extensive interaction with felodipine is expected. A recent study in eight volunteers, however, reported a 28% relative reduction in felodipine bioavailability (lowering absolute bioavailability to about 10%), when OCBZ (900 mg/day) was co-administered for 1 week (Zaccara et al., 1993). The clinical relevance of this interaction has yet to be defined.

EFFECTS OF AEDs ON OCBZ

Preliminary observations, based on a retrospective study, showed that enzyme-inducing drugs such as PB and PHT do not induce MHD formation but can increase its oxidative conversion to DHD. This has been considered to be clinically insignificant and to represent a minor pathway in OCBZ metabolism (Kumps and Wurth, 1990). The ratio between MHD concentrations (mg/L) and the OCBZ oral doses (mg/kg) was reported to be lower in a group of adult patients receiving comedication with enzyme-inducing drugs (mean value 0.74) compared with patients receiving OCBZ alone (mean value 0.94), indicating that some interaction with enzyme-inducing co-medication may occur. When OCBZ was combined with VPA, the ratio was 0.93, similar to that found in monotherapy (van Parys et al., 1991).

A comparison of OCBZ and MHD kinetics in normal subjects and in patients treated with other AEDs has been published (Tartara et al., 1993). Three groups of eight subjects (drug-free healthy controls and epileptic patients receiving chronic treatment with either PB or VPA alone) each received a single oral dose of OCBZ 600 mg. Plasma concentrations of OCBZ and MHD were followed for up to 48 h. The areas under the curve (AUCs) of OCBZ and MHD were significantly lower in patients receiving PB than in controls, whereas no differences were found between patients receiving VPA and controls. The mean values of MHD terminal half-life were 20 h in controls, 17 h in patients receiving PB, and 24 h in patients receiving VPA. These data suggest that the modifications caused by enzyme-inducing drugs such as PB and PHT should have modest consequences on OCBZ dosing; even the association with VPA should not require any adjustment of OCBZ oral dosages.

EFFECTS OF OTHER DRUGS ON OCBZ

Verapamil inhibits the metabolism of CBZ to an extent that can produce clinical manifestations of CBZ neuro-

toxicity. If the two agents are used concomitantly, some authors suggest halving the dose of CBZ to avoid clinical toxicity (Macphee et al., 1986; Beattie et al., 1988).

The potential interaction of verapamil and OCBZ was studied in 10 healthy volunteers (Kramer et al., 1991). After titration of OCBZ to 900 mg/day, verapamil (240 mg/day) was administered for a week. The AUC of MHD decreased by 20% compared with the baseline, but for OCBZ it remained unchanged, and for DHD was reduced by 50%. Reduction of DHD concentration is probably due to inhibition of MHD oxidation, but the MHD reduction remains to be explained. This interaction is likely to be negligible in most cases, and OCBZ could be an alternative to CBZ in patients receiving concomitant verapamil therapy.

Cimetidine interacts with many drugs (Somogyi and Muirhead, 1987) causing clinical toxicity in some patients receiving PHT (Kutt, 1989); for chronic treatment, CBZ clearance does not appear to be significantly influenced by cimetidine, and no modification of oral dosages is usually required (Sonne et al., 1983; Levine et al., 1985); VPA clearance can be reduced by cimetidine, but the reduction is small and the clinical significance undefined (Webster et al., 1984). The cimetidine–OCBZ interaction was studied in eight volunteers; cimetidine treatment 800 mg/day for a week did not significantly modify the pharmacokinetics of OCBZ or MHD (Keränen et al., 1992*a*).

Erythromycin is one of the macrolide antibiotics most frequently implicated in pharmacokinetic drug interactions (Periti et al., 1992). Commonly, toxic signs appear shortly after erythromycin administration and resolve rapidly after withdrawal of the antibiotic, suggesting that the inhibition mechanism is direct competition for the enzyme. Concomitant treatment with CBZ results in a sharp increase of CBZ concentrations with related toxicity (Ketter et al., 1991*a*,*b*). Patients receiving chronic CBZ treatment should be warned to avoid erythromycin.

Results of an eight-volunteer study indicated that OCBZ offers a clinical advantage over CBZ when coadministration of erythromycin is required (Keränen et al., 1992*b*). A week of erythromycin therapy (1,000 mg/day) had no influence on the pharmacokinetic parameters of OCBZ and its active metabolite MHD. Erythromycin, however, decreased the AUC of DHD by about 50%. The clinical implications of this interaction should be negligible, as suggested by the authors, as only 4–5% of MHD is metabolized to DHD.

Dextropropoxyphene can interfere with major AEDs (Dam et al., 1980), but the entity and clinical significance of individual interactions varies. For CBZ, the interaction leads to important clinical toxicity (Dam et al., 1977). A recent study shows the effects of dextropropoxyphene on the kinetics of OCBZ and its metabolites in eight patients with epilepsy or trigeminal neuralgia receiving chronic OCBZ treatment (Mogensen et al., 1992). Plasma concentrations of MHD were not significantly affected by dextropropoxyphene (195 mg/day for 1 week), even if the DHD concentrations were reduced as a possible consequence of inhibited MHD oxidation. OCBZ is therefore a valuable alternative to CBZ if co-administration of dextropropoxyphene is envisaged.

A clinically important interaction has been described between viloxazine, a bicyclic antidepressant, and both CBZ (Pisani et al., 1984, 1986) and PHT (Pisani et al., 1992). A double-blind, placebo-controlled study in six epileptic patients receiving chronic OCBZ monotherapy (1,200–1,400 mg/day) showed that a 10-day add-on treatment with viloxazine had no significant influence on OCBZ plasma concentrations. The concentrations of the MHD metabolite were increased by 10%; DHD concentrations decreased by an average of 31% (Pisani et al., 1991). As suggested for the other interactions, this effect is probably due to inhibition of MHD oxidation caused by viloxazine co-administration. No adverse effects were reported in any patients. It was concluded that viloxazine can be used safely in depressed epileptic patients receiving OCBZ treatment.

CONCLUSIONS

We present a summary of the published data on OCBZ interactions (Table 2), compared with interactions of other AEDs. Considering that some of the data on OCBZ interactions are retrospective or have been obtained in healthy volunteers after acute or short-term administration (and therefore need confirmation in patients receiving chronic therapy), the number of published investigations is above average for a new AED. Compared with the traditional AEDs (Table 1), OCBZ has a favorable profile, with a reduced potential for drug interactions. Other new AEDs are (or soon will be) available, and the features of OCBZ are comparable to those of some of the most promising compounds (Table 3).

A low potential for drug interactions is particularly useful for a newly marketed AED, as part of its initial clinical use will be in difficult-to-treat patients already receiving therapy with one or more enzyme-inducing AEDs. In this case, the addition of OCBZ should not cause significant kinetic interactions. The substitution of an inducing agent with OCBZ, however, should be carefully monitored because of possible de-induction, and the oral doses of associated drugs should then eventually be reduced.

Similarly, interactions with concomitant non–AEDs

TABLE 2. *Metabolic interactions of oxcarbazepine*

Interaction	Effect	Subjects	Reference
Effect of oxcarbazepine on:			
Antipyrine	Slight metabolic induction or no metabolic effect	Healthy volunteers, patients with epilepsy and with trigeminal neuralgia	Larkin et al., 1991 Hulsman et al., 1987 van Emde Boas et al., 1989 Patsalos et al., 1990
Phenytoin	No significant effect	Epileptic patients	Houtkooper et al., 1987
Valproate	No significant effect	Epileptic patients	Houtkooper et al., 1987 Battino et al., 1992
Warfarin	No effect	Healthy volunteers	Kramer et al., 1992
Felodipine	Bioavailability reduction (−28%), significantly less than with inducing AED (−94%)	Healthy volunteers	Zaccara et al., 1993
Oral contraceptives	Significant metabolic induction, similar to other inducing AED	Healthy volunteers	Klosterskov Jensen et al., 1992
Effect on oxcarbazepine by:			
Phenobarbital and phenytoin	Slight induction of MHD oxidation, effect lower than with other AED	Epileptic patients	Kumps and Wurth, 1990 van Parys et al., 1991 Tartara et al., 1993
Valproate	Slight inhibition of MHD elimination or no effect	Epileptic patients	van Parys et al., 1991 Tartara et al., 1993
Verapamil	20% reduction of MHD AUC clinical significance?	Healthy volunteers	Kramer et al., 1991
Cimetidine	AUC of MHD practically unmodified	Healthy volunteers	Keränen et al., 1992*a*
Erythromycin	AUC of MHD practically unmodified	Healthy volunteers	Keränen et al., 1992*b*
Dextroprophoxyphene	AUC of MHD practically unmodified	Patients with epilepsy or trigeminal neuralgia	Mogensen et al., 1992
Viloxazine	10% increase in MHD AUC, clinical significance?	Epileptic patients	Pisani et al., 1991

AED, antiepileptic drug; AUC, area under curve plasma concentrations vs. time; MHD, 10,11-dihydro-10 hydroxycarbazepine.

should be modest. The modifications of OCBZ kinetics caused by other drugs seem of little, if any, clinical significance. The effects of OCBZ on the clinical efficacy of other drugs should theoretically be a minor problem compared with some of the traditional AEDs, except for the reduced efficacy of oral contraceptives.

Very often, interactions between AEDs and drugs used to treat other medical disorders are already known, and can be avoided by using alternative, noninteracting drugs. Unfortunately, not all general practitioners and specialists in other medical fields are familiar with the specific interactions and, in some cases, tend to neglect or to overemphasize the problem. Even if a clinically significant interaction is not suspected, patients frequently solicit additional consultations or therapeutic drug monitoring when a drug is added to their usual regimen. Apart from the clinical implications, these situations lead to an increase in the total costs of health care, in terms of both time and money.

For these reasons, the availability of AEDs that have limited and thoroughly evaluated drug interactions would greatly simplify treatment. The summarized data on OCBZ suggest that it has limited drug interactions, but a definite picture will emerge only after more extended clinical use.

TABLE 3. *Pharmacokinetic interactions of the new antiepileptic drugs (AEDs)*

Drug	Possible influence on AED plasma level by		Influence of AED on plasma level of other drug	
	Inducing drugs	Inhibiting drugs	Reduction	Increase
Oxcarbazepine	No	No	Yes	No
Lamotrigine	Yes	Yes	No	Yes
Vigabatrin	No	No	Yes	No
Gabapentin	No	No	No	No
Felbamate	Yes	No	Yes	Yes

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Oxcarbazepine: Experience and Future Role

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Oxcarbazepine in Affective and Schizoaffective Disorders

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Anticonvulsants have been successfully used in pharmacopsychiatry after their therapeutic value in affective and schizoaffective disorders had been documented in several clinical trials. As the authorities in several countries registered newer anticonvulsants with fewer side effects, their therapeutic value in psychiatric disorders was studied. Clinical studies from the early 80's onward have demonstrated the efficacy of oxcarbazepine (OCBZ), a keto derivative of carbamazepine, in treating mania in affective and schizoaffective disorders. In addition, OCBZ has a distinct pharmacokinetic profile concerning drug-drug interactions compared to carbamazepine and other anticonvulsants. Therefore, the value of OCBZ in the treatment of affective and schizoaffective disorders needs to be evaluated. We reviewed the literature with regard to pharmacokinetic and pharmacodynamic characteristics of OCBZ, drug-drug interactions relevant in pharmacopsychiatry, and the clinical effects of OCBZ in the treatment of patients with affective and schizoaffective disorders. According to the literature, OCBZ is regarded as effective in acute mania and appears to reduce the dosage of neuroleptics required for the treatment of affective and schizoaffective disorders. In addition, it has a preferable pharmacokinetic profile with less severe side effects compared to carbamazepine and neuroleptics. Furthermore, since OCBZ does not interact substantially with the cytochrome P450 enzyme system, co-administration with neuroleptics or antidepressants appears to be well tolerated in affective disorders. However, despite promising effects of OCBZ, few clinical studies have been published in the last 15 years. We conclude that further studies should validate the efficacy of OCBZ in treating mania and evaluate possible pharmacopsychiatric indications as well as limitations for this psychotropic compound.

Anticonvulsants in affective disorders

The antimanic and prophylactic effect of lithium administration in patients with affective and schizoaffective disorders is regarded as one of the most important discoveries of pharmacopsychiatry. However, several problems have remained unresolved: specifically, the partial- or non-responsiveness of approximately 30% of the patients with affective and up to 70% of patients with rapid-cycling or schizoaffective psychosis was evident [72]. Furthermore, lithium therapy produced significant side effects and, resulting from this, non-compliance. Thus, the introduction of anticonvulsants in the pharmacological treatment of affective and schizoaffective disorders was an important advancement, since these compounds apparently have a lithium-like clinical activity profile [71]. Historically, the first anticonvulsant medication used in psychoses was diphenylhydantoin. Its psychotropic, especially mood-stabilizing effect was observed in the 1940s [44]. Dipropylacetamide, an amide of valproate, was subsequently shown to have antimanic efficacy and a supportive effect with neuroleptics [53,54]. Dipropylacetamide produced a sizable prophylactic efficacy, especially if combined with lithium [73,89]. A similar efficacy in the treatment of mania could be demonstrated for valproate [26].

In parallel, *Takezaki* and *Hanaoka* [81] found that the anticonvulsant carbamazepine improved endogenous mania in patients with organic psychoses. *Okuma* et al. [67,68] subsequently reported a strong effect of carbamazepine in treating acute manic symptoms and a prophylactic efficacy in patients with bipolar affective disorders. However, international attention to these findings did not occur until 1980, when *Ballenger* and *Post* [4] demonstrated the antimanic properties of carbamazepine under controlled circumstances.

These studies initiated the introduction of carbamazepine and valproate as mood-stabilizing drugs in affective and schizoaffective psychoses. Additionally, certain antidepressive effects of carbamazepine and valproate were described (for review, see [19]) and other psychiatric indications of these compounds have become apparent. Nevertheless, in the prophylactic treatment of patients with major affective disorders, especially classical bipolar disorder, lithium was more effective than carbamazepine [37,39] and was accompanied by a reduced risk of suicide [63,84]. However, carbamazepine and even more so valproate were beneficial in the treatment and prevention of rapid-cycling and acute mania [27,59,60]. Furthermore, carbamazepine was superior to valproate and lithium in preventing schizoaffective disorder [26,38].

Possible future indications of carbamazepine (which appears to be relevant concerning the possible use of oxcarbazepine in psychiatric patients) are the adjunctive treatment of schizo-

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phrenic patients [34,65,74] and the treatment of personality disorders [33], especially where symptoms of aggressive or impulsive behavior are present [40,46,61]. Also, it should be noted that carbamazepine appears to be the drug of choice in the treatment of abstinence symptoms in the discontinuation of benzodiazepine-treatment in abusers [56,76].

Clinical findings for both the well-established anticonvulsant carbamazepine and valproate initiated investigations on the efficacy of newer anticonvulsants in producing antimanic, antidepressive, and mood-stabilizing effects in affective and schizoaffective disorders. In particular, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine, acetazolamide, neuropeptides such as TRH, neuropeptide Y and cholezystokinine have been investigated (for review, see [20,72]).

Oxcarbazepine in affective disorders

Although the effect of oxcarbazepine (OCBZ) was already described in the early 80's, its development as an antimanic and mood-stabilizing compound was not immediately realized despite its apparent superior pharmacodynamic and pharmacokinetic performance when compared with carbamazepine [15,21,50,75]. Particularly, a sizable number of adverse reactions following carbamazepine treatment had been observed clinically (such as nausea, headache, diplopia, dizziness and drowsiness). It was suspected that at least some of these side effects and adverse reactions were not due to the primary compound, but to partially active and potentially toxic metabolites, especially the epoxide of carbamazepine [21,62], which may amount to approx. 5–10% of the carbamazepine concentration. To circumvent the synthesis of carbamazepine epoxide and cope with the above metabolic problems, OCBZ, the keto derivative of carbamazepine at position 10 of the tricyclic molecule, was developed. Since this 10-keto derivative is already oxidized, the microsomal P450-related oxidation is inhibited and OCBZ is directly reduced to the monohydroxy derivative (MHD), which is regarded as the active compound [30].

Consequently, the question was raised as to whether OCBZ would show similar psychotropic effects compared to carbamazepine, and furthermore, whether the profile of side effects produced by carbamazepine would be improved by preventing carbamazepine epoxide formation. Investigations on the safety and efficacy of OCBZ have been summarized by *Grant* and Faulds [36]. This review demonstrated that side effects of carbamazepine which required drug withdrawal were indeed reduced in their incidence and intensity after replacement by OCBZ. However, investigations on the efficacy of OCBZ in pharmacopsychiatry are presently limited (see Table 1 for studies on the antimanic effects of OCBZ): Most of the work on the use of OCBZ in affective disorders was performed by *Emrich* et al. [22,23,25–27]. Following the hypothesis of involvement of GABAergic mechanisms in the clinical effects of anticonvulsants in affective disorders [24], *Emrich* et al. first described an antimanic effect of OCBZ [26,27], which appeared to be comparable to the antimanic effect of valproate. The average reduction of the initial IMPS-values (Inpatient Multidimensional Psychiatric Scale [57]) was 49.9±26.1% for OCBZ (one-tailed Wilcoxon-test: $p < 0.01$; maximum dosage range: 1.8–2.1 g/d) compared to 49.6±36.6% for valproate ($p < 0.05$; maximum dosage range: 1.8–3.8 g/d) [26,27].

Further support of this first clinical evidence was provided by investigations of *Müller* and *Stoll* [62] in a multicenter study with OCBZ in mania. Here, 48 patients were treated with dosages up to 2.1 g/d (one patient was given 3 g/d), with a good therapeutic result observed in 83%, and a good tolerance (no adverse reactions) in 94% of the patients. Only 3 patients who received the highest clinical dosages reported dizziness, nausea, itching, double vision, or increased restlessness. In another controlled clinical trial by these authors [62], 20 patients were investigated for a two-week period and randomly allocated to either OCBZ (0.9–1.2 g/d) or haloperidol (15–20 mg/d). Manic symptoms measured on the BRMAS [5] decreased in both groups (from 20 to 8 in two weeks), with the onset of action slightly faster in the OCBZ group – after one week, the BRMAS dropped from 20 to 11 in the OCBZ group and from 20 to 13 in the haloperidol group. Unfortunately, the varying side effect profiles were not reported in this study. However, they compared the side effects of a single-dose application of 600 mg OCBZ compared to 400 mg carbamazepine in healthy subjects, and reported less „dizziness" for OCBZ ($n = 10$) compared to carbamazepine ($n = 10$). Further information on side effects of OCBZ is summarized in Table 2.

Another report in 1984 focused on the use of OCBZ in mania and schizophrenic symptoms: *Velikonja* and *Heinrich* [88] performed an open investigation with OCBZ in 10 patients suffering from a manic syndrome or schizoaffective psychosis using 900 mg/day OCBZ in combination with neuroleptics. All 10 patients revealed a decrease of psychotic symptoms. Furthermore, manic symptoms, "hostility", and "paranoid syndrome", measured with a factor-analysis of the AMDP-diagnostic system [29], were reduced more significantly than with haloperidol monotherapy. In addition, the dose of neuroleptics needed to reduce manic and schizophrenic symptoms in the OCBZ group was about half of the amount compared to a matched control-group ($n = 10$) without additional OCBZ treatment (12.3 versus 24.9 mg/d average haloperidol dosage). This concurs with later findings by *Raptis* et al. [74], demonstrating a supportive effect of carbamazepine on neuroleptic treatment of psychotic symptoms in schizophrenic patients.

A larger cohort of patients was investigated by *Emrich* et al. [22,23] in a multicenter trial of OCBZ versus haloperidol in acute mania. 42 patients were enrolled, 19 of whom could finally be evaluated in each treatment group. Average improvement within the first week appeared to be more rapid with haloperidol compared to OCBZ. After two weeks, the effect of the two drugs on mania ratings was comparable. This effect was obtained with a mean dose of haloperidol of 42 mg/d compared to 2.4 g/d of OCBZ, which is pharmacodynamically equivalent to a carbamazepine dose of about 1.6 g/d. OCBZ tolerability was significantly better. The incidence of side effects was 3.5 times as high in the haloperidol group as in the OCBZ group. In particular, muscular stiffness, Parkinsonism, apathy, loss of libido, lactation, eye cramps, and extrapyramidal effects were more evident in the haloperidol group.

In a second multicenter study comparing OCBZ with lithium in acute mania [22,23], the lithium-induced reduction of mania scores tended to be slightly faster within the first week, but after two weeks, there was no difference between the two treatments in this respect. The therapeutic effects were reached

Table 1 Clinical studies on the antimanic effects of oxcarbazepine (OCBZ).

	Patients	Study design	OCBZ/X	Dosages	Duration of Treatment	Scale	Therapeutic response	Side effects
Emrich et al. 1984 + 1985 [26, 27]	Multiple psychosis	Double-blind controlled, variable ABA-design	OCBZ/ valproate n = 7/n = 5	OCBZ: 1.8 – 2.1 g/d VPS: 1.8 – 3.8 g/d	Variable	IMPS [57]	Significant reduction of mania for both groups: OCBZ: 49.9% ($p < 0.01$) VPS: 49.6% ($p < 0.05$)	No major side effects reported
Müller & Stoll 1984 [62]	Multiple psychosis	Open multi-center study	OCBZ n = 48	Up to 2.1 g/d Some patients 3 g/d	?	?	83% with "good therapeutic results"	Significant adverse reaction in 3/48 patients with the highest clinical dosage (see text)
	Multiple psychosis	Controlled multicenter trial, randomized	OCBZ/haloperidol n = 28/ n = 10	OCBZ: 0.9 – 1.2 g/d Haloperidol: 15 – 20 mg/d	14 days	BRMAS [34]	Reduction of mania from 20 to 8 in 14 days in both groups; faster anset for OCBZ (after 7 days: 11 comp. to 13 for haloperidol)	
Velikonja & Heinrich 1984 [88]	Manic syndrome in mania, schizoaffective psychosis or schizophrenia	Open pilot study, OCBZ-augmentation to haloperidol	OCBZ/Ø n = 10/n = 10 +haloperidol	0.5 g/d fixed dose of OCBZ in combination with haloperidol adjusted to the severity of symptoms	15 days t.i.d.	AMDP-rating scale [29], factor analysis	Reduction of psychotic symptoms in both groups; in the OCBZ-group only 12.3 mg/d haloperidol (comp. to 24.9 mg/d in the controls) was needed. Better reduction of mania and "hostility" in the OCBZ-group	OCBZ was "well tolerated"
Emrich 1990 + 1994 [22, 23]	Acute manic syndrome	Multicenter trial	OCBZ/ haloperidol n = 19/n = 19	OCBZ: initial dosage 0.9 g/d; mean dosage 2.4 g/d Haloperidol: initial dosage 15 mg/d; mean dosage 42 mg/d	15 days t.i.d.	BRMAS [5]	Reduction from 21 to 9 for OCBZ and from 22 to 7 for haloperidol after 15 days	Incidence of side-effects 3.5 times less in the OCBZ group (see text)
	Acute manic syndrome	Multicenter trial	OCBZ/ lithium n = 28/n = 24	OCBZ: initial dosage 0.9 g/d; mean dosage 1.4 g/d Lithium: mean dosage 1.1 g/d	15 days t.i.d.	BRMAS [5]	Reduction from 28 to 11 for OCBZ and from 27 to 10 for lithium after 15 days	Comparable tolerability

with the relatively low dose of 1.4 g/d OCBZ compared to a lithium dosage of 1.1 g/d. Tolerability was also comparable in both groups. However, since certain patients do not tolerate lithium and/or are non-compliant in lithium treatment, OCBZ appears to have certain advantages over lithium. Therefore, OCBZ may be regarded as a suitable alternative to haloperidol or lithium in acute mania.

Regarding a possible antidepressive efficacy of OCBZ, two studies described "antidepressant-like" effects using learned helplessness and forced swimming tests in rats [6, 43]. No clinical studies, however, were currently available.

The prophylactic effect of OCBZ was investigated by *Cabrera* et al. [11]. In a small group of patients, the authors compared the prophylactic effect of OCBZ with lithium prophylaxis in a long-term randomized clinical trial in bipolar and schizoaffective patients. With regard to this small cohort of patients (n = 8 for OCBZ), they found that no valid conclusions about the prophylactic effects of OCBZ were possible at that time. However, the frequency and intensity of manic as well as depressive episodes decreased under OCBZ treatment. In addition, OCBZ appeared to be better tolerated than lithium in this small group of patients [11, 12]. Three years later, the prophylactic efficacy of OCBZ in affective disorders was also investigated by *Wildgrube* [90]. She did not find any prophylactic efficacy of oxcarbazepine. However, the study revealed certain limitations. The author noted that the two groups of patients (lithium, n = 7 vs. OCBZ, n = 8) were not comparable concerning age and severity of illness. Additionally, some of the OCBZ patients were non-responders to lithium, and there was a high dropout rate in the OCBZ group, as patients became aware that OCBZ was not officially approved in affective disorders. Furthermore, the dosage of OCBZ might have been too low, as

there was only limited experience on OBCZ dosing in bipolar disorders at that time.

Pharmacokinetic and pharmacodynamic considerations with oxcarbazepine

OCBZ is the 10-keto analogue of carbamazepine, but has a pharmacokinetic profile that differs distinctively from carbamazepine. The mechanism of action of OCBZ is not sufficiently known, but its similarity in structure and clinical efficacy to carbamazepine suggests that its mechanism of action may involve inhibition of voltage-dependent sodium action potentials [58] as well as GABA receptor increase [72].

As the main active metabolite of OCBZ, 10,11-dihydro-10-hydroxycarbamazepine (MHD) is produced by enzymatic reduction rapidly after a nearly complete oral absorption, elimination half-life of OCBZ is short, calculated as between 1 to 5 hours [18, 52, 83]. Accordingly, only minimum amounts of the parent drug are to be found in the peripheral blood [30]. Elimination half-life of MHD was reported to be up to 26.5 hours [83, 87]. The enzymes involved in processing MHD are reported to be non-inducible. Elimination of MHD occurs via direct renal excretion, glucuronidation, and to a small extent by hydroxylation to a dihydroxy derivative (DHD) [30]. Glucuronidation of MHD is performed by UDP-glucuronosyl transferases that, in contrast to microsomal oxidases, are less sensitive to induction or inhibition. As the transformation of MHD to DHD depends on the $P450_{IIIA}$ isoenzyme of the cytochrome P450 family, administration of OCBZ may affect contraception since the main metabolic pathway for estrogens also appears to be conducted by the $P450_{IIIA}$ isoenzyme [3]. Another possibility of pharmacokinetic interaction might be the level of plasma protein binding of an antiepileptic drug. The protein binding of MHD is only 40% [47], suggesting only a limited possibility of kinetic interactions. In contrast to CBZ, there is no established "therapeutic window" for OCBZ [36]. Therefore, monitoring plasma concentrations of OCBZ or MHD may only be useful in cases of intoxication.

The side effect profile of OCBZ appears to be similar in nature to that of carbamazepine, although frequency and severity of side effects have been shown to be slightly less. However, the incidence of "severe" side effects leading to withdrawal of the study medication was significantly less [16, 41, 75], e.g. 13/94 for OCBZ compared to 25/100 for carbamazepine in previously untreated patients with epilepsy [16]. Nevertheless, studies directly comparing OCBZ and carbamazepine are still limited. The most common dose-related side effects of OCBZ were somnolence, headache, dizziness, nausea and fatigue (for review, see [36, 78, 82]). Further relevant side effects in different clinical studies are described in Table 2.

Two studies have shown no impairment of cognitive function with OCBZ monotherapy [1, 13]. To our knowledge, there are no reports of persisting negative effects of OCBZ on hematological parameters so far, either. Furthermore, hematological parameters affected by carbamazepine medication have been reported to reach normal levels after switching to OCBZ therapy [42]. However, isolated cases of hyponatremic coma have been reported [80], so electrolyte abnormalities should be closely monitored. Fortunately, OCBZ-induced hyponatremia is rarely of clinical significance [15, 86].

The very low level of hepatic cytochrome P450 enzyme induction by OCBZ is of great advantage. Nevertheless, OCBZ may interact with other drugs relevant to the treatment of psychiatric patients, which is demonstrated as follows (regarding the interactions with major psychotropic drugs and in Table 3 regarding further relevant compounds).

Antidepressants

Concurrent drug treatments with mood-stabilizers and antidepressants are not uncommon in affective disorders. Conventional drugs such as phenytoin or carbamazepine have been found to reduce serum drug levels and to change the clinical response to psychotropic drugs. Low antidepressant serum levels induced by carbamazepine may be reversed by treatment with OCBZ, leading to an appropriate clinical response. Leinonen and co-workers [55] have found this effect in two patients treated with the selective serotonin-reuptake inhibitor citalopram, concomitantly, when switching from carbamazepine to OCBZ. In addition, contrary to carbamazepine, OCBZ does not induce the CYP2C subfamily enzyme, which catalyzes the parent drug, citalopram [79]. Pisani et al. [70] demonstrated that viloxazine, a second-generation antidepressant, produced a small increase of MHD without clinical implications, as viloxazine inhibits the conversion to DHD, which is only a minor pathway of MHD degradation. This drug interaction might be observed in other newer antidepressants as well.

Lithium

To our knowledge, there is only one publication concerning the co-administration of lithium and OCBZ [12]. In one patient with a bipolar affective disorder of several years duration, lithium carbonate and OCBZ were combined without any adverse effects. In the 22 months of follow-up after initiating this therapy, a sufficient steady clinical response without adverse reaction was observed.

Neuroleptics

There are only very few published results on drug interactions between carbamazepine and neuroleptics, or even between OCBZ and the latter. A reduction of haloperidol plasma levels at up to 50% has been reported following concomitant carbamazepine therapy [45]. *Tiihonen* et al. [85] examined 14 patients who were treated with clozapine and thioridazine during carbamazepine treatment, which was subsequently switched to OCBZ. In all 14 patients, clozapine levels were 40 – 50% lower during carbamazepine therapy compared to the OCBZ treatment period. The corresponding decrease of thioridazine levels during CBZ treatment was less evident. As the present results show that OCBZ does not induce neuroleptic metabolism, unwanted drug interactions may be avoided by administering OCBZ instead of carbamazepine.

Discussion

Anticonvulsants have moved into an important position as alternatives and adjuncts to lithium and neuroleptics in the treatment of affective and schizoaffective disorders. The main advantages of anticonvulsants are their superior tolerance and greater safety with regard to possible intoxication in acute and prophylactic treatment of these disorders. In addition, combi-

Table 2 Reported adverse effects (AEs) of oxcarbazepine (OCBZ).

Side-effect	Study	Study design	Comment
Skin eruption	*Beran* 1993 [7]	Case report (n = 3)	Cross-reactive skin eruption when switching from carbamazepine to OCBZ because of exfoliative dermatitis (3/3)
Hyponatremia	*Nielsen* et al. 1988 [66]	Cross-sectional study, 21/41 patients were found to be hyponatremic	Authors found a non-significant trend towards increasing frequency of hyponatremia with increasing age of patients
	Pendlebury et al. 1989 [69]	Open study (n = 15)	Dose dependent reduction in plasma sodium levels in 12/15 patients
	Borusiak et al. 1998 [9]	Case report (n = 1). Retrospective study	12-year old girl with severe clinically relevant hyponatremia (118 mmol/l) and hypochloremia (81 mmol/l). Effect reversible after discontinuation of OCBZ and treatment with CBZ. 9/48 children had clinically non-apparent hyponatremia retrospectively
Dizziness, vertigo	*Emrich* 1990, 1994 [22, 23]	Double-blind, placebo-controlled study on OCBZ in 6 patients	At 2100 mg/dl of OCBZ these side-effects did occur in one case
Vomiting, lack of coordination, parkinsonism		Multicenter trial OCBZ vs. haloperidol including 37 patients in both groups	AEs in the OCBZ group were rare: vomiting in one case, lack of coordination in one patient and a Parkinson-like syndrome in one patient
Dizziness, nausea, sedation, fatigue, somnolence	*Friis* et al. 1993 [32]	Retrospective multicenter study (n = 947)	AEs in 597 (350) OCBZ monotherapy (polytherapy) patients were as follows: dizziness 4(11)%, sedation 4(9)%, fatigue 5(7)%, nausea or vomiting 2(5)%, visual disturbances 2(5)%, headache 2(4)%, ataxia 2(2)%, amnesia 2(1)%, vertigo 2(1)%
	Christe et al., 1997 [14]	Prospective, controlled study (n = 249), VPA vs. OCBZ 1:1	OCBZ related AEs: somnolence 15%, weight increase 12%, fatigue 12%, headache 10%, dizziness 10%, alopecia 8%, nausea 8%, abdominal pain 6%
	Bill et al. 1997 [8]	Prospective, controlled study (n = 287), PHT vs. OCBZ 1:1	AEs in OCBZ group: somnolence 30%, headache 14%, dizziness 13%, nausea 9%
	Schachter et al. 1999 [77]	Double-blind, placebo-controlled study (n = 102)	AEs in OCBZ group vs. placebo group: headache 20/20%, dizziness 18/12%, somnolence 16/0%, nausea 20/6%, fatigue 10/2%
Leukopenia, light ataxia, rashes	*Wildgrube* 1990 [90]	Prospective open study, comparing OCBZ (n = 8) with lithium (n = 7) in affective disorders	In the OCBZ group temporally rashes were observed in 3 patients, slight ataxia was mentioned in 2 cases at the beginning of the study. Mild leucocytopenia was found in the OCBZ group generally
Rare side-effects	*Gatzonis* et al. 1999 [35]	Case report (n = 1)	Case report of an oxcarbazepine-induced oculogyric crisis after vagus nerve stimulation
	Bülau et al. 1998 [10]	Case report (n = 1)	Infant born with mild facial dysmorphism (mother on 900 mg OCBZ during pregnancy).

Table 3 Reported interactions of oxcarbazepine with other drugs.

Drug	Study/Subjects	Effect	Comment	References
Ethinylestradiol	13 healthy women	Significant metabolic interaction	Suspected induction of $P450_{IIA}$ isoenzyme by OCBZ	*Klosterskov-Jensen* et al. 1992 [48]
	16 healthy women, randomized double-blind crossover design	Significant induction of ethinylestradiol and levonorgestrel metabolism		*Fattore* et al. 1999 [31]
Verapamil	Co-administration of OCBZ and verapamil in 10 healthy volunteers	20% decrease in the Cmax and AUC of 10,11-dihydro-10-hydroxy-carbamazepine, unchanged AUC of OCBZ	Clinical relevance of this interaction is unclear	*Krämer* et al. 1991 [51]
Felodipine	450 mg bid in 8 healthy volunteers	28% decrease in the systemic availability of felodipine	Clinical relevance of this interaction is unclear	*Zaccara* 1991 [91]
Viloxazine	Randomized, double-blind cross-over placebo controlled trial in 6 epileptic patients on fixed dosage of OCBZ	11% increase in plasma concentration of MHD and 31% fall in DHD. OCBZ plasma concentration were unaffected by viloxazine	No changes in seizure frequency or signs of drug toxicity were observed	*Pisani* et al. 1994 [70]

nation therapy with anticonvulsants may help to reduce the required dosage of other medications, for example, neuroleptics in acute mania [64]. Furthermore, they also appear to substantially reduce the side effects (such as Parkinsonism) of neuroleptic medication, and concomitantly enhance the efficacy of these medications [74].

Combination therapy with anticonvulsants and lithium has been shown to reduce side effects and enhance the efficacy of prophylactic and acute treatment strategies in affective disorders [20,28,72]. These aspects also improve patient compliance, and therefore lead to a better outcome of these disorders. Recently, the good clinical treatment response to carbamazepine and valproate has led to further investigations with newer anticonvulsants, and possible indications in other psychiatric disorders made anticonvulsants more attractive for pharmacopsychiatry. However, one of the interesting compounds with regard to the use in psychiatric disorders, OCBZ, appears to be underrepresented, although it displays a number of advantages over other anticonvulsants. Initial clinical experience with OCBZ has been made with good clinical results concerning efficacy, drug-safety and tolerability in the 80's – patients appeared to better tolerate OCBZ than carbamazepine [41,75]. Regarding anticonvulsive efficacy as one major factor of the clinical effect in affective disorders [28], OCBZ, as a keto derivative of carbamazepine, has the advantage that the knowledge about carbamazepine may be partially used for considering the use of OCBZ in psychiatric disorders.

Furthermore, it has a major pharmacokinetic advantage over carbamazepine, as it induces less hepatic enzymes, especially microsomal cytochrome P450 related enzymes. As MHD, the main active metabolite of OCBZ, has a low degree of protein binding, only few relevant pharmacokinetic interactions in complex treatment regimens may appear. Despite these possible advantages, only limited numbers of investigations examining the use of OCBZ in psychiatric disorders currently exist. Most of these studies examined the antimanic efficacy (6 studies, compare Table 1), while just two studies focussed on prophylactic effects in affective disorders, and no clinical study has investigated the possible antidepressive properties of OCBZ to date. Whereas studies examining prophylactic effects were insufficient to draw any conclusions, the antimanic effect of OCBZ was demonstrated to be comparable to that of haloperidol [22,23,62,88], lithium [22,23], and valproate [26,27]. Augmented to haloperidol, the dosage of haloperidol needed for antimanic treatment could be reduced, and thus the amount of unwanted side effects was also significantly lowered [88]. As a consequence of this, the compliance of the patients is expected to be much better than with neuroleptics alone. Furthermore, this type of therapy is non-sedative and, apparently, from a psychopathological point of view, acts more "specifically" than neuroleptics on the core symptoms of mania [27]. Some studies investigated the clinical efficacy and side effects of OCBZ compared to other anticonvulsants or placebo in patients with epilepsy (see Table 2). These studies indicate a better side effect profile of OCBZ compared to phenytoin [8] and a "comparable" tolerability regarding valproate [14], but more side effects than placebo [77]. Studies comparing OCBZ with lamotrigine, gabapentin or topiramate are not available at present.

The prophylactic effectiveness of OCBZ has been controversially discussed [11,90], and a possible antidepressive effect has not yet been researched. Nevertheless, the clinical profile and possible future indications of OCBZ offer promise in the therapy of psychiatric disorders. Velikonja and Heinrich [88] have shown that OCBZ combined with neuroleptics in psychotic patients with manic and schizophrenic symptoms produced a pronounced reduction of neuroleptic dosage required for the clinical control of productive symptoms. The amount of neuroleptics needed was about half of the amount when combined with OCBZ at 900 mg/day. This concurs with findings of Raptis et al [74], who demonstrated the adjunctive effect of carbamazepine on neuroleptic medication in affective and schizoaffective disorders, and the data of Müller-Oerlinghausen et al. [64] concerning the augmentation of valproate on neuroleptic medication in acute mania.

A clinical use for the combination of OCBZ and antidepressants can only be hypothesized, as there have currently been no such investigations documented. From a theoretical point of view, this interaction may occur as a combination of two types of mood regulatory mechanisms in the CNS. These are (i) the amygdaloid-temporal lobe regulatory mechanisms [2,17], and (ii) the major mechanisms of thymoleptic therapy on, for example, brainstem and cortical neurons and neurotransmitter systems such as the noradrenergic, dopaminergic, and serotonergic systems. We pointed out that the combination of targeting these two types of modes of action in the regulation of affect may be of great advantage [19]: (i) one advantage may be the multimodal targeting of depression itself performing a more-than-additive antidepressive effect if combining these compounds, and (ii) another advantage is the reduction of side effects since serum levels of OCBZ as well as antidepressants may be below the normal therapeutic levels when these drugs are combined. Therefore, future studies should not only validate the antimanic efficacy, but should also investigate the possible prophylactic and antidepressive effects.

With regard to these results and possible future indications the question has to be raised, why only a few studies were performed during the last 15 years. According to Krämer [49], licensing was delayed in several countries due to insufficient statistical evidence of the efficacy and limited amount of data on safety of OCBZ during the 80's. The high daily costs of OCBZ (more than double) compared to the equivalent dose of carbamazepine may have been another reason. These aspects and results from several studies finding lithium advantageous to carbamazepine in affective disorders [37,39] might also have slowed its development as a useful compound in psychiatric disorders. This may change in the following years, as an increasing number of studies providing more data on the safety and efficacy in epilepsy have now led to a licensing by the authorities for mono- and add-on-therapy in more than 50 countries.

Conclusions

The conclusions are that oxcarbazepine is effective in the treatment of acute mania and in reducing the dosage of neuroleptics required to treat affective and schizoaffective disorders. In addition, it has a preferable pharmacokinetic profile with fewer side effects than some other anticonvulsants. Since OCBZ does not interact substantially with the cytochrome P450-enzyme system, co-administration with neuroleptics or antidepressants might, according to preliminary results, be

well tolerated in affective and schizoaffective disorders. Further studies should evaluate possible indications as well as limitations for this psychotropic compound.

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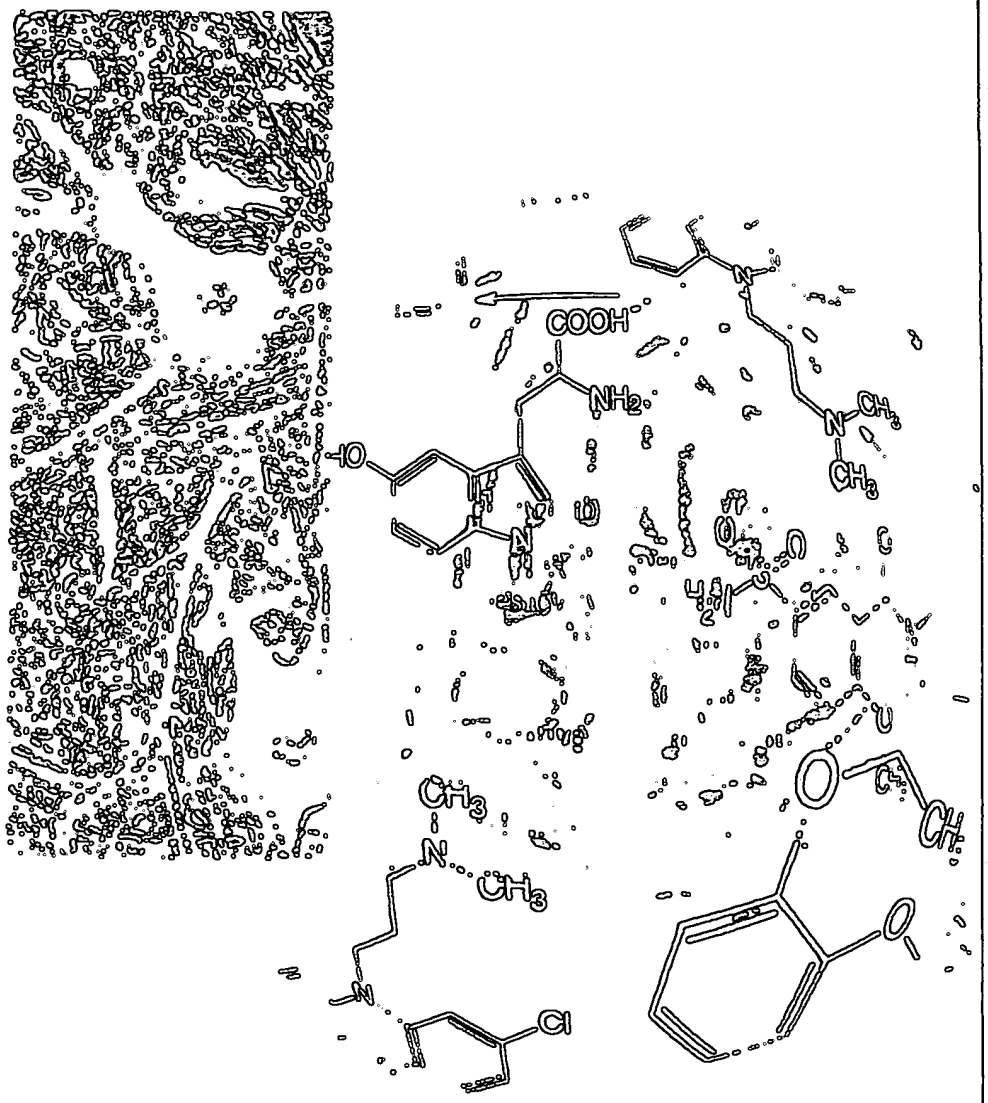

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CLINICAL

Treating Bipolar Disorder: Toward the Third Millennium

by Alan J. Gelenberg, M.D., and Heather S. Hopkins

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(This is the second in a two-part series on treating bipolar disorder. The first part ran in February Psychiatric Times -Ed.)

Although lithium is still the only drug approved by the U.S. Food and Drug Administration for both the treatment of acute mania and the maintenance treatment of bipolar disorder (BD), it is not efficacious for many people with BD, and its side effects are problematic for many others. The search for alternative treatments for the 20% to 40% of "classic" patients who do not respond adequately to lithium or cannot tolerate it continues. Nonclassic patients (for example, rapid-cyclers, patients with mixed and dysphoric mania, and those with comorbid substance abuse) seem even less likely to respond adequately to lithium. Because a minority of patients with BD remain euthymic on lithium alone, adjunctive treatments are also being studied. Investigators are also trying to determine which antidepressant medication is best for treating bipolar depression without triggering a switch into mania.

In addition, clinical trials have shown that the atypical

antipsychotics clozapine (Clozaril) and risperidone (Risperdal) have shown promise as treatment for mania, as have less conventional treatments, such as calcium channel blockers and omega-3 fatty acids. In contrast with prescribing practices in many other countries, where doctors primarily use lithium, many doctors in the United States are prescribing these newer therapies before rigorous studies have proven their effectiveness.

Atypical Antipsychotics

Haloperidol (Haldol) and other typical antipsychotics can rapidly diminish symptoms of mania. They are often used in conjunction with lithium for severe psychotic symptoms and acute behavioral excitement during an acute manic episode. Many patients are maintained for long periods on conventional antipsychotics, even though their efficacy in maintenance treatment has never been demonstrated and the risk of tardive movement disorders appears high.

An alternative may be to use an atypical antipsychotic. A retrospective study by Guille et al. (2000) found clozapine, risperidone and olanzapine (Zyprexa) to be equivalent in efficacy in the treatment of BD when used concomitantly with mood stabilizers. Of note, 25% of the patients gained more than 20 lbs over three months. Substantial weight gain (over 10 lbs) was significantly greater in olanzapine-treated patients.

Clozapine. Research has shown that clozapine may be effective for acutely manic and psychotic patients, especially those who are treatment resistant and/or intolerant of other drugs, and for those with rapid-cycling BD (Barbini et al., 1997; Frye et al., 1996; Zarate et al., 1995a, 1995b). But while clozapine is relatively free from extrapyramidal side effects and the risk of tardive dyskinesia, it is associated with a number of serious toxic reactions, including agranulocytosis, seizures and cardio-respiratory complications.

Risperidone. Case reports and open studies suggest that risperidone is efficacious in acute mania. A subgroup of patients with BD may benefit from adjunctive risperidone during acute mania and for maintenance treatment (Ghaemi and Sachs, 1997; Ghaemi et al., 1997). There have been some reports of risperidone inducing mania or worsening manic symptoms (Sajatovic et al., 1996; Schnierow and Graeber, 1996).

Olanzapine. Open studies have indicated that olanzapine is efficacious for patients with mania and treatment-resistant BD (McElroy et al., 1998; Zarate et al., 1998). In a three-week, double-blind trial, Tohen and colleagues (1999) found olanzapine to be significantly superior to placebo for acute mania. In a four-week, double-blind study that used a higher starting dose, Tohen

and colleagues (2000) again found olanzapine to have greater efficacy than placebo in patients with acute mania. In March 2000, the FDA approved olanzapine as a treatment for acute mania in BD.

Ziprasidone. This medication was approved by the FDA in February for the treatment of schizophrenia. Ziprasidone (Geodon) also is being studied for the treatment of BD.

Calcium Channel Blockers

A recent consensus survey of psychiatric experts classified nimodipine (Nimotop) as an alternative and nimodipine and other calcium channel blockers as adjuncts-to other mood stabilizers for treatment-resistant mania (Sachs et al., 2000). Verapamil (Calan, Isoptin) had been reported to be comparable to lithium and superior to placebo for acute mania in anecdotes, small case series and a few small, double-blind trials (Garza-Treviýo et al., 1992; Dubovsky et al., 1986). More recent, larger randomized controlled trials found it inferior to lithium (Walton et al., 1996), however, and not superior to placebo (Janicak et al., 1998). It might be considered as an adjunct for occasional patients unresponsive to or intolerant of more standard treatments.

Omega-3 Fatty Acids

Recent evidence suggests that the consumption of omega-3 fatty acids, which are found primarily in fish oil, may have beneficial effects for patients with BD. In one study, patients with BD who took fish oil supplements did better over six months than patients who took placebo: only two (13%) of 16 suffered relapses compared to 11 (52%) of 21 assigned to placebo (Nidecker, 1998). In a double-blind, randomized, placebo-controlled trial, Stoll and colleagues (1999) evaluated the subacute mood-stabilizing properties of omega-3 fatty acids as an adjunctive treatment in patients with unstable BD. Concomitant medications included carbamazepine (Tegretol), gabapentin (Neurontin), lithium, divalproex (Depakote) and a number of benzodiazepines and antidepressants. Patients who took the omega-3 fatty acid supplement had a significantly longer period of remission than those who took placebo. The same apparent benefit from omega-3 fatty acids was observed in eight patients who were taking no other concomitant mood-stabilizing drugs.

Bipolar Depression

The depressed phase of BD is still an area much in need of study. Antidepressants may speed up mood cycling and trigger mania, especially the tricyclic antidepressants (TCAs). For this reason, antidepressants are often avoided when a patient with BD

experiences a mild depression. Many doctors simply check the levels of the patient's mood stabilizer, employ psychosocial interventions and wait. When depression is more severe, antidepressants, such as bupropion (Wellbutrin), selective serotonin reuptake inhibitors, a monoamine oxidase inhibitor or electroconvulsive therapy (ECT) are usually used. The risk of suicide should be assessed in these cases and hospitalization considered. After the depressive episode is over, the antidepressant should be continued for only a few weeks, rather than the six to 12 months it would be in nonbipolar depression. Bupropion and the SSRIs appear to be less likely than TCAs to precipitate a switch into mania in patients with bipolar depression.

Other Medications

In addition to the therapies listed above, preliminary tests have been conducted with the following approaches, which might merit additional study: the reversible acetylcholinesterase inhibitor donepezil (Aricept) (Burt et al., 1999); the dietary supplement choline (Stoll et al., 1996); the adenylate cyclase inhibitor demeclocycline (Roitman et al., 1998); and the protein kinase C inhibitor (and anti-estrogen) tamoxifen (Nolvadex) (Bebchuk et al., 1998).

Nonpharmacologic Treatments

ECT. This treatment should be considered for acute mania and bipolar depression in patients who require a rapid response, cannot tolerate or be exposed to medication, or do not respond to medication. It has been associated with remission or marked clinical improvement in approximately 80% of ECT-treated manic patients described in the medical literature (Mukherjee et al., 1994). Bilateral ECT may be more efficacious than unilateral ECT for bipolar patients in a depressive episode, and a dosage over twice the initial seizure threshold may bring about more rapid improvement of depressive symptoms.

Psychotherapy. The exact role of psychotherapy in the treatment of patients with BD has yet to be definitively established. For most bipolar patients, psychotherapeutic approaches combining cognitive, interpersonal, behavioral, family-focused and psychoeducational components can be useful in enhancing compliance and diminishing recurrences when combined with pharmacotherapy. At the very least, patients need to be involved with their treatment. Patients in a sustained relationship with a psychotherapeutically oriented clinician are more likely to tolerate adverse effects of medication, work with the doctor to find optimum drug levels, and report early symptoms of recurrence. They are also less likely to drop out of treatment.

Conclusion

For patients with BD who do not respond to or cannot tolerate lithium, there are now many alternatives. Few, however, have adequate scientific support of their benefit in a large number of patients, in long-term treatment and in medication combinations. It seems prudent at this stage to use an evidence-based approach, starting with the medications whose efficacy is best established by large, rigorously designed trials. Treatment needs to be tailored to the individual patient, based on personal and family history of response and characteristics of the illness. Polypharmacy may be the answer for many patients, and psychotherapy can help provide long-term stability. The multicenter, collaborative Systematic Enhancement Program for Bipolar Disorder (STEP-BD) project, sponsored by the National Institute for Mental Health, may help sort out treatment options.

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Metabolism of two new antiepileptic drugs and their principal metabolites *S*(+)- and *R*(−)-10,11-dihydro-10-hydroxy carbamazepine

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Abstract

BIA 2-093 and BIA 2-059 are two stereoisomers under development as new antiepileptic drugs. They act as prodrugs for the corresponding hydroxy derivatives (*S*(+)- or *R*(−)-10,11-dihydro-10-hydroxy carbamazepine, respectively) which are known to be the active metabolites of the antiepileptic drug oxcarbazepine (OXC). The purpose of this study was to define the metabolic pathway especially in terms of stereoselectivity, and to estimate the possibility of racemization in humans. For in vivo studies, the rat, mouse and rabbit were chosen as models in order to cover a broad spectrum of metabolic activity. In addition, incubations with liver microsomes from these three species plus dog and monkey were compared to results obtained with human liver microsomes. It was found that both drugs were almost instantly hydrolysed to the corresponding 10-hydroxy compounds in mice, rats and rabbits. Mice and rabbits were not able to oxidize the 10-hydroxy compounds to OXC in significant amounts. In the rat, BIA 2-093 also gave origin to OXC, whereas BIA 2-059 resulted in the formation of OXC and the *trans*-diol metabolite in equal amounts. It could be shown that the rat is able to reduce the formed OXC in liver to *S*(+)-10-hydroxy metabolite, resulting in a loss of enantiomeric purity after treatment with BIA 2-059 rather than in the case of BIA 2-093. Human liver microsomes hydrolysed BIA 2-093 and BIA 2-059 to their corresponding 10-hydroxy compounds and to OXC in a very small extent with BIA 2-093 only. Therefore, BIA 2-093 and BIA 2-059 seem to be preferable drugs over OXC since they most likely exhibit a 'cleaner' metabolism. From a therapeutic point of view BIA 2-059 would be less appropriate than BIA 2-093 for the purpose of treating epileptic patients due to its propensity to undergo inactivation to the *trans*-diol.

Keywords: Antiepileptic; Metabolism; Stereoselective; Oxcarbazepine; Microsomes

1. Introduction

Epilepsy affects 1% of the world population (Sander and Shorvon, 1987). Despite recent advances that led to the appearance of several new

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antiepileptic drugs (Upton, 1994; Perucca, 1996), a staggering 25% of cases in industrialized countries are still uncontrolled. The existing compounds are quite inadequate for a large number of patients, because of intractability of seizures or serious side effects (Davies-Jones, 1988). This encourages the development of more selective and less toxic antiepileptic drugs.

Carbamazepine (CBZ) has been the compound of choice in the past (Morselli, 1995), although it has several side effects including nausea, headache, dizziness, diplopia (Hoppener et al., 1980) and rash in 2–4% of the patients (Ramsay et al., 1983). This is apparently related to the formation of the carbamazepine-10,11-epoxide metabolite, catalysed by the CBZ-inducible P-450 isoform CYP3A4 (Kerr et al., 1994). This main metabolite is further converted by a microsomal epoxide hydrolase into a pharmacologically inactive racemate of *trans*-diol enantiomers. Because of these problems with toxicity and induction, a keto analogue of carbamazepine had been synthesized (oxcarbazepine, OXC) that is readily metabolized in humans to 10-hydroxy-CBZ and then to the *trans*-diol derivative, thus preventing the formation of the epoxide metabolite (Baltzer and Schmutz, 1978; Feldmann et al., 1978). Still, OXC is endowed with the same type of side effects, but with less severity (Rogvi-Hansen and Gram, 1995). Its potency has been reported to be less than that of CBZ (Houtkooper et al., 1987).

BIA 2-093 and BIA 2-059, (−)-(10*S*)- and (+)-(10R)-10-ace-to-xy-10,11-dihydro-5H-dibenz [b,f]azepine-5-carboxamide, share with CBZ and OXC the dibenzazepine nucleus bearing the 5-carboxamide substituent, but are structurally different at the 10,11-position (Fig. 1). These two enantiomers were synthesized with the aim of maintaining high anticonvulsant capability, preventing the formation of toxic epoxide metabolites and avoiding unnecessary production of enantiomers or diastereoisomers of metabolites and their conjugates (Benes et al., 1999). They both possess anticonvulsant properties with very similar pharmacodynamic profiles (Benes et al., 1999).

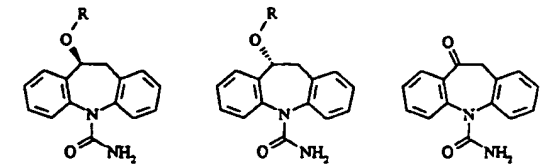

Fig. 1. Chemical structures of relevant drugs and metabolites.

Although it is known that OXC forms both the *S*(+)- and *R*(−) enantiomer of the 10-hydroxylated metabolite in humans in a ratio of ~4:1 (Schütz et al., 1986), it is uncertain whether the oxidation back to OXC is preferred by one of these enantiomers. For the development of enantiomeric drugs, this information is of major importance, since the formation of OXC will then result in an enantiomeric dilution. Furthermore, it is not known if the enzymes catalysing the formation of the *trans*-diol metabolite prefer one of the 10-hydroxy isomers. Since the *trans*-diol metabolite is inactive, its formation will result in a shortened pharmacological action of the drug.

The aim of this study was to obtain pharmacokinetic data of BIA 2-093, BIA 2-059, their respective 10-hydroxy derivatives and OXC individually in order to get a better picture of the reaction kinetics involved in the metabolism of these compounds. Furthermore, using pure enantiomers allows conclusions concerning the stereoselectivity of these processes. The rat was chosen as one of the in vivo models because the oxidation to OXC is a major process in this specie, and the results were compared to mice and rabbits. In vitro studies with liver microsomes were done to allow qualitative predictions for the metabolism in humans.

2. Methods

2.1. Animals and treatment

Adult male Wistar rats, obtained from Harlan-Interfauna (Barcelona, Spain) and weighing between 180 and 280 g, were used. Rats were kept eight per cage under controlled environmental conditions (12 h light/dark cycle, room temperature 22 ± 1°C and humidity 50 ± 5%). Food and tap water were allowed ad libitum and the experiments were all carried out during daylight hours.

Male CD1 mice (Charles River, 25–30 g), obtained from the animal house of the Instituto Gulbenkian de Ciência (Oeiras, Portugal) and female New Zealand rabbits (3.5–4 kg) from Criffa, S.A. (Barcelona, Spain) were kept under the same conditions as the rats. All animals were fasted the night before treatment. The drugs, suspended in carboxymethylcellulose as carrier vehicle (0.5% w/v, 4 ml/kg animal weight), were administered orally via stomach tube. For rats, BIA 2-093, BIA 2-059, *S*(+)- and *R*(−)-10-OH-CBZ and OXC were all administered at 20 mg/kg, and blood, liver and brain samples were taken after 0.25, 0.5, 1, 2, 4 and 24 h (four animals at each time point). Mice were treated with 20 mg/kg BIA 2-093 and BIA 2-059 and blood, liver and brain samples taken after 0.5, 1 and 4 h ($n=4$). Only blood samples were collected from treated rabbits (20 mg/kg) at 1 and 4 h after oral administration ($n=3$).

2.2. Chemicals

BIA 2-059 [(+)-(*R*)-10-acetoxy-10,11-dihydro-5H-dibenzo[b,f]azepine-5-carboxamide], BIA 2-093 [(−)-(*S*)-10-acetoxy-10,11-dihydro-5H-dibenzo/b,f/azepine-5-carboxamide], (+)-(*S*)- and (−)-(*R*)-10,11-dihydro-10-hydro-xy-5H-dibenzo[b,f]azepine-5-carboxamide (*S*(+)- and R(−)-10-OH-CBZ), the racemate (±)-10,11-dihydro-10-hydroxy-5H-dibenzo[b,f]azepine-5-carboxamide (10-OH-CBZ), the racemate (±)-10,11-dihydro-10,11-dihydro-xy-5H-dibenzo[b,f]azepine-5-carboxamide (*trans*-diol), 10,11-dihydrocarbamazepine (used as internal standard) were all synthesized in the Laboratory of Chemistry, BIAL, with purities > 99.5%. Oxcarbazepine was supplied by Farchemia (Italy). Sodium pentobarbital was obtained from Sigma (St Louis, MO) and dissolved in saline (3% w/v) for i.p. administrations.

2.3. Sample treatment

Blood was taken from the vena cava of rats and mice and from the ear vein of rabbits, respectively, stabilized with one drop of heparin in the syringe and kept on ice until centrifuged at 3000 × *g* for 15 min (4°C). Of the supernatant plasma phase 1 ml was added to 1 ml of 0.1 M sodium phosphate buffer (pH 5) spiked with 2 μg/ml 10,11-dihydrocarbamazepine as internal standard.

These samples were then added to LiChrolut RP-18 SPE columns (3 ml, 200 mg, Merck) which were conditioned before with 1 ml acetonitrile, 2 ml water/acetonitrile (95:5) and 2 × 2 ml water. After eluting the plasma sample, the columns were allowed to equilibrate for 2 min and then washed with 2 ml water and 2 ml water/acetonitrile (95:5). After drying the sorbent under airflow for 5 min the remaining was eluted with 2 × 250 μl acetone, the solvent evaporated at 35–40°C (Centrivac, Heraeus Instruments) and the residue reconstituted in 1 ml HPLC mobile phase.

Liver and brain tissues were dissected after taking the blood and stored in 20 ml plastic scintillation vials at −100°C until use. After thawing and weighing, 0.1 M sodium phosphate buffer (pH 5) was added to the organs (10 ml to liver, 5 ml to brain) and the samples homogenized using a Heidolph DIAX 900 mixer. The homogenates were transferred to 10 ml plastic centrifugation tubes, i.e. the complete brain homogenate (~7 ml) and 10 ml of the liver suspension, respectively. Centrifugation at 15000 × *g* for 20 min at 4°C gave clear supernatants of which 1 ml is added to 1 ml of 0.1 M sodium phosphate buffer (pH 5) spiked with 2 μg/ml internal standard and then proceeded with solid phase extraction as described for plasma samples.

2.4. In vitro assays

BIA 2-093, 10-OH-CBZ (both enantiomers and as racemate) and OXC were incubated with rat and human liver microsomal preparations. In addition, BIA 2-093 was incubated with mouse, rabbit, dog and primate liver microsomes in order to determine possible variations between species. Pooled human liver microsomes were obtained from Gentest (Woburn, MA), dog and monkey microsomes were provided by Quintiles (Scotland) and rat, mouse and rabbit microsomes were pre-

pared by differential centrifugation. Protein concentration was determined by the method of Lowry et al. (1951) for the dog and primate preparations and by the method of Bradford (1976) for rat, mouse and rabbit using Bio-Rad protein assay dye reagent (Bio-Rad Laboratories, Richmond, CA). Incubation mixtures consisted of 100 μM test compound in 50 mM potassium phosphate buffer (pH 7.4) and were carried out at 37°C in the presence and absence of metabolic cofactors. These cofactors consisted of 25 mM glucose-6-phosphate, 2 mM $NADP^+$ and 6 units/ml glucose-6-phosphate dehydrogenase, Type VII from Bakers yeast, dissolved in 1 ml 2% $NaHCO_3$ (0.04 ml per 2 ml incubation when added). The total volume was maintained between 1.75–2.00 ml and the protein content of the final incubation solution was 1 mg/ml in all cases. Reactions were initiated with the addition of the test compound after a preincubation time of 3 min at 37°C. Samples of 125 μl were removed at various time points (1, 2, 5, 10 and 30 min) and transferred into 2 ml plastic tubes containing the same volume of acetonitrile to stop the reaction. After centrifugation (Biofuge, Heraeus Instruments) for 5 min at 16000 × *g* (room temperature), 20 μl of the supernatant was directly injected onto the HPLC system.

2.5. HPLC-MS analysis

Sample analysis was performed using LC-MS (HP 1100 Series, Agilent Technologies) with atmospheric pressure electrospray (AP-ES) ionization (positive ion detection). In parallel, UV spectra were recorded with a diode array detector (monitoring wavelength was set to 210 nm). The separation method was adapted from Hartley et al. (1991) and performed on an EcoCART 125-3, LiChrospher 100 RP-18 column (5 μm, Merck) with a 4 × 4 mm guard column containing the same stationary phase. The mobile phase was an isocratic mixture of water/methanol/acetonitrile (62:25:13), freshly prepared for each analysis, filtered (0.22 μm, NL 16, Schleicher & Schuell) and degassed (USB) with a flow of 0.8 ml/min. Injection volume was 20 μl. A time programmed selected ion monitoring (SIM) with two masses for each compound of interest was selected for MS detection: 0–8 min *m/z* 293 + 294 (*trans*-diol metabolite), *m/z* 277 + 278 (10-OH-CBZ) and 275 + 276 (OXC), 8–11 min *m/z* 319 + 320 (BIA 2-093 or BIA 2-059), 11–16 min *m/z* 239 + 261 (internal standard). The fragmentor energy was set to 100 V for maximal detection sensitivity for these compounds. Further settings included: capillary voltage 3500 eV, nebulizer gas temperature 350°C and nebulizer pressure 40 psi. The limit of quantification for BIA 2-093 and its stereoisomer was 17 ng/ml and the ones for the other analytes were between 8 (10-OH-CBZ) and 20 ng/ml (OXC). Retention times ranged from 2 min for the *trans*-diol derivative to 12 min for the internal standard.

For chiral separations a LiChroCART 250-4, ChiraDex (β-cyclodextrin, 5 μm) column from Merck was employed and protected by a LiChroCART 4-4, ChiraDex (β-cyclodextrin, 5 μm, Merck) guard column. The mobile phase was water/methanol (80:20) with a flow of 0.8 ml/min (injection volume: 20 μl). The 10-OH-CBZ as well as the *trans*-diol racemate could be sufficiently separated (resolution > 1.5) with this method.

3. Results

3.1. Metabolism and elimination of BIA 2-093 in the rat

The metabolic profile and the elimination rate of BIA 2-093 in plasma is shown in Fig. 2. The parent compound was metabolized extremely fast and could not be detected at the first data point 15 min post dose. It was transformed mainly to OXC and to a minor extent to the hydrolysis product 10-OH-CBZ. Further oxidation to the *trans*-diol metabolite was found to occur only to a very small extent, approx. 1% of the OXC formation when considering the $AUC_{0-24\ h}$ (Table 1).

In contrast to that observed in plasma, in rat brain, OXC was accumulated less efficiently than the hydroxy metabolites and this tendency was even more evident in liver (Fig. 2), where the $AUC_{0-24\ h}$ of 10-OH-CBZ was almost twice compared to OXC (Table 1).

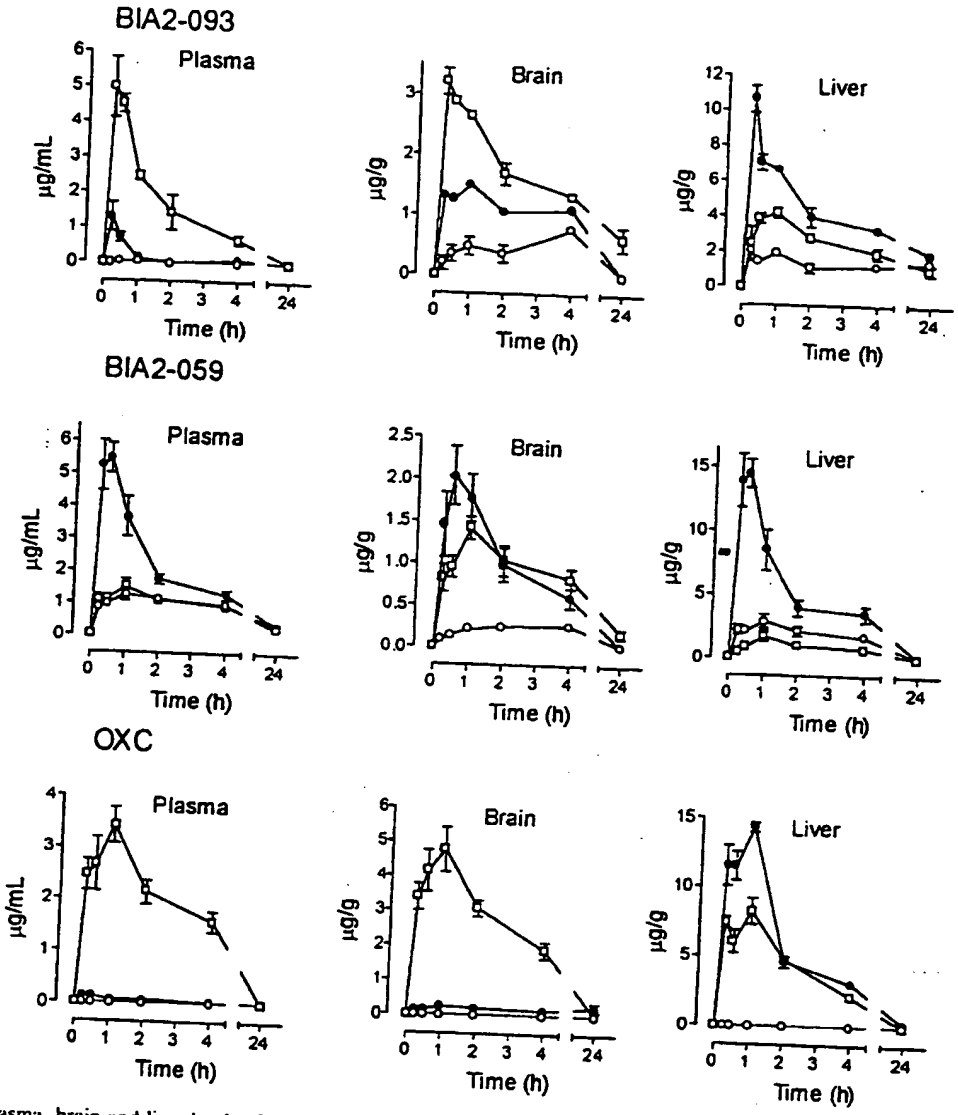

Fig. 2. Rat plasma, brain and liver levels of parent compound and metabolites after a single oral dose of 20 mg/kg BIA 2-093, BIA 2-059 and OXC, respectively ($n = 4$, mean ± SEM). 10-OH-CBZ (●), OXC (□) and *trans*-diol (○).

3.2. Metabolism and elimination of BIA 2-059 in the rat

As BIA 2-093, its enantiomer BIA 2-059 was rapidly metabolized and no parent compound could be detected after 15 min. (Fig. 2). But in this case, metabolism led to the 10-OH-CBZ as the major product and the *trans*-diol was formed in substantial amounts comparable to OXC. A very similar pattern could be found in liver and only in brain an increased accumulation of OXC led to different AUC ratios (Table 1).

3.3. Treatment with OXC, S(+)- and R(−)-10-OH-CBZ

In agreement with previously published results (Feldmann et al., 1978, 1981), the plasma levels in OXC treated rats reflected a very slow metabolism of this compound in which the reduction to 10-OH-CBZ seems to be the only transformation (Fig. 2). Levels of OXC and its metabolites in brain samples paralleled their corresponding levels in plasma. In liver, 10-OH-CBZ could be found at high concentrations, with c_{max} almost twice as high as c_{max} for OXC.

After administration of S(+)- or R(−)-10-OH-CBZ, the observed metabolic profile was very similar to that in BIA 2-093 and BIA 2-059 treated rats (Table 1). The S(+)-enantiomer, which equals the hydrolysis product of BIA 2-093 when assuming a chirality preserving transformation, was very rapidly oxidized to OXC and only in liver the parent compound could be detected in equal amounts. In contrast, the R(−)-isomer (the hydrolysis product of BIA 2-059) was relatively stable and only slowly oxidized to OXC and the *trans*-diol, both in similar amounts. As in the case of BIA 2-059 treated rats, the metabolic profile was very similar in plasma and liver, and only brain tissue showed a relative accumulation of OXC.

Table 1
AUCs of drugs and their metabolites in rat. The bioavailability of metabolites after a single oral 20 mg/kg administration of BIA 2-093, BIA 2-059, S(+)- and R(−)-10-OH-CBZ and OXC in rat are expressed as $AUC_{0\text{-}24\ h}$ in μg/h ml (plasma) or μg/h/g (brain and liver). The amounts of BIA 2-093 and BIA 2-059 were below the detection limit in all cases

Treatment Sample	*Trans*-diol	10-OH-CBZ	OXC
BIA 2-093			
Plasma	0.1	1.7	14.4
Brain	9.4	15.5	27.2
Liver	31.5	71.7	41.7
BIA 2-059			
Plasma	16.1	26.2	16.9
Brain	3.9	10.8	14.2
Liver	26.0	60.8	12.2
S(+)-10-OH-CBZ			
Plasma	0.1	1.6	19.2
Brain	0.3	3.0	19.1
Liver	2.1	33.4	32.1
R(−)-10-OH-CBZ			
Plasma	20.3	37.4	21.7
Brain	0.6	18.1	19.1
Liver	32.8	86.7	13.1
OXC			
Plasma	0.0	0.5	24.8
Brain	0.0	4.9	31.6
Liver	0.0	61.1	41.1

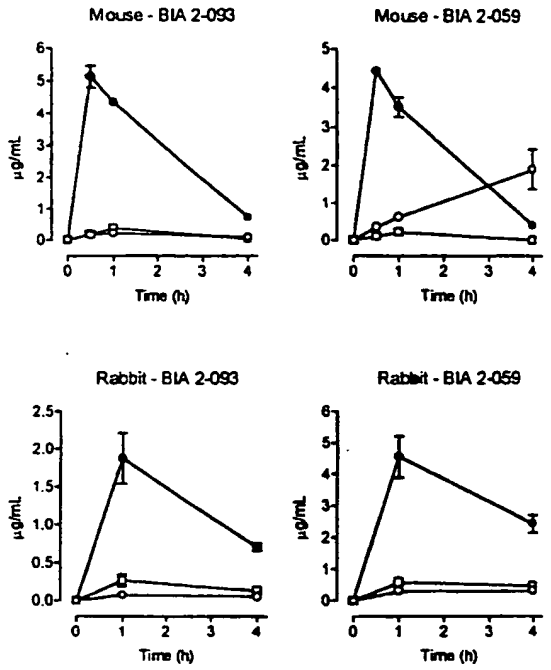

Fig. 3. Metabolic profile of BIA 2-093 (a) and BIA 2-059 (b) in mouse ($n = 4$) and rabbit ($n = 3$) plasma after a single oral dose of 20 mg/kg (mean ± SEM). 10-OH-CBZ (●), OXC (□) and *trans*-diol (○).

3.4. Metabolism in mice and rabbits

In mice, BIA 2-093 was very rapidly hydrolysed to S(+)-10-OH-CBZ (no parent compound could be detected at 30 min post dose) and, in contrast to metabolism in rats, further oxidation to OXC did not take place to a significant extent (Fig. 3). The elimination rate of 10-OH-CBZ from plasma was comparable to that of OXC in rats, i.e. after 4 h the concentration decreased to less

than 15% of the level at 0.5 h. The same profile could be found for the stereoisomer BIA 2-059, with the exception that here the *trans*-diol metabolite was formed in significant amounts, being the major metabolite at > 3 h (Fig. 3).

Rabbits seem to have an absorption/metabolism/elimination behaviour very similar to mice with two exceptions. First, after treatment with BIA 2-093, the hydrolysis product *S*(+)-10-OH-CBZ reached plasma levels (c_{max} = 1.9 μg/ml) only approximately half of those in equally treated mice. This is also true when comparing with *R*(−)-10-OH-CBZ plasma levels in both mice and rabbits after treatment with BIA 2-059 (c_{max} is 4–5 μg/ml at 0.5 h). The second difference is that BIA 2-059 was not metabolized to the *trans*-diol in notable amounts and concentrations were even lower than those of OXC.

3.5. In vitro metabolism

3.5.1. Human liver microsomes

All incubations resulted in a relatively slow hydrolysis of BIA 2-093 (half life $t_{0.5}$ = 20 min) and BIA 2-059 ($t_{0.5}$ = 35 min). Only with BIA 2-093, OXC could be detected in trace amounts after 2 h. Accordingly, when starting with the 10-OH-CBZ racemate or the enantiomers individually, no metabolism could be detected over the duration of the experiment except for the very slow oxidation of the *S*(+)-enantiomer (near the detection limit of the method). OXC itself exhibits a reduction to 10-OH-CBZ with an initial formation rate of 0.7 μmol/mg protein/min and an isomeric *S*(+):*R*(−) ratio of ~3.5:1. This transformation was not detectable in incubations without cofactors.

3.5.2. Rat liver microsomes

In contrast to human liver microsomes, hydrolysis of BIA 2-093 and BIA 2-059 was completed within 2 min. OXC was formed in significant amounts (3.8 μmol/mg protein/min) as well as lower amounts of the *trans*-diol metabolite (0.8 μmol/mg protein/min). These formation rates were both constants for at least 30 min. Except for the initial hydrolysis step, no reaction could be detected in the absence of cofactors. The metabolic profile of the 10-OH-CBZ enantiomers (as racemate or individually) was almost identical to that found with BIA 2-093 and BIA 2-059. When starting with OXC, minor transformations to *S*(+)-10-OH-CBZ and *trans*-diol were observed (0.1 and 0.2 μmol/mg protein/min, respectively).

3.5.3. Other species

BIA 2-093 incubations with mouse, rabbit, dog and monkey liver microsomes all exhibited a very similar picture to the one obtained with human liver microsomes, i.e. no metabolism beyond the initial non-enzymatic hydrolosis. Only rabbit microsomes catalyzed the formation of the *trans*-diol metabolite at a low rate (0.3 μmol/mg protein/min).

3.6. Chiral analysis

To obtain information concerning the stereoselectivity of the observed biotransformations, selected samples from treated rats and mice as well as from in vitro studies were analysed using a chiral stationary phase (Fig. 4). It was found that both species reduced OXC in the liver only to the *S*(+)-isomer of 10-OH-CBZ and, therefore, no racemization occurred if the animal was treated with this isomer or BIA 2-093. In contrast, in animals treated with BIA 2-059 or *R*(−)-10-OH-CBZ, the enantiomeric purity decreased slowly due to the oxidation to OXC and the following mentioned reduction to the *S*(+)-isomer. This enantiomeric dilution was negligible in mice because of the extremely slow oxidation to OXC in this species. The formation of the *trans*-diol was only detectable in significant amounts after administration of the *R*(−)-isomer and this oxidation was enantioselective in both rats and mice. However, the absolute configuration of the *trans*-diol metabolite could not be determined due to a lack of standard compounds.

4. Discussion

Both BIA 2-093 and its stereoisomer BIA 2-059 were extremely rapidly metabolized in all three

species studied (rat, mouse and rabbit) to their corresponding hydroxy derivatives *S*(+)- and *R*(−)-10-OH-CBZ, respectively. In the rat, this was followed by an oxidation to OXC (in the case of BIA 2-093) or to the *trans*-diol metabolite and OXC (in the case of BIA 2-059). According to previously published data (Feldmann et al., 1978, 1981), the rat is not able to metabolize OXC to a significant amount. However, the results of this study show that indeed in rat liver a significant reduction to the hydroxy derivative occurs. This reduction is reversed rapidly resulting in diminishing amounts of 10-OH-CBZ in plasma. Altogether, this indicates that the rat not only possesses the responsible reducing enzymes (probably the cytosolic arylketone reductase as in humans) in amounts and activities comparable to other species, but is also able to reverse this reaction very effectively, in contrast to mice and rabbits. Therefore, after hydrolysis of BIA 2-093 and BIA 2-059, the corresponding 10-OH-CBZ metabolites are very stable in those two species, whereas in rat the formation of OXC is clearly the predominant pathway. This suggestion is supported in most part by results from the in vitro studies. Metabolism of BIA 2-093 by liver microsomes was clearly species dependent in the sense that OXC could be detected as a major metabolite only with rat liver microsomes. With microsomes derived from all other species, the non-enzymatic hydrolysis to 10-OH-CBZ was the only significant transformation.

The in vivo stability and further transformation of the 10-OH-CBZ metabolite in rat is stereoselective and the same is true for the reduction of OXC in the rat liver. After treating rats with *S*(+)-10-OH-CBZ, this isomer was rapidly oxidized and the $AUC_{0-24\ h}$(OXC):$AUC_{0-24\ h}$ (parent) ratio is 12 in plasma (Table 1). On the other hand, after treatment with the *R*(−)-enantiomer, this ratio was 0.58 and very similar to the $AUC_{0-24\ h}$ (*trans*-diol):$AUC_{0-24\ h}$ (parent) ratio of 0.54. This indicates that *R*(−)-10-OH-CBZ is the only source for significant amounts of the *trans*-diol metabolite. The AUC ratios were very similar (8.5 and 0.65) after treating the animals with the 10-OH-CBZ precursor compounds BIA 2-093 and BIA 2-059, respectively, which is another indication for an extremely fast hydrolysis without any effect on the following metabolic transformations. The de-acetylation probably occurs already during absorption in the gastrointestinal tract. In vitro studies also showed that this hydrolysis is non-enzymatic and can be detected almost instantly when adding the drugs to rat plasma (data not shown).

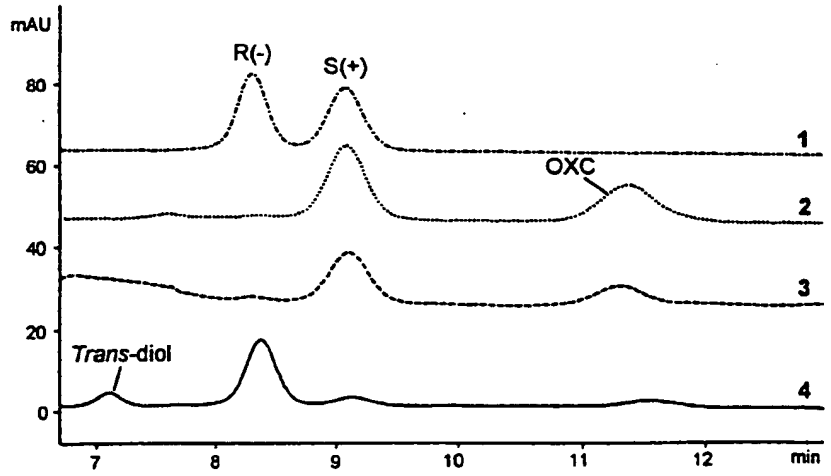

Fig. 4. Chiral HPLC separations of racemic 10-OH-CBZ standard solution (1) and selected samples of differently treated rats (all 1 h after a 20 mg/kg oral dose): (2) OXC, liver; (3) *S*(+)-10-OH-CBZ, plasma and (4) *R*(−)-10-OH-CBZ, plasma.

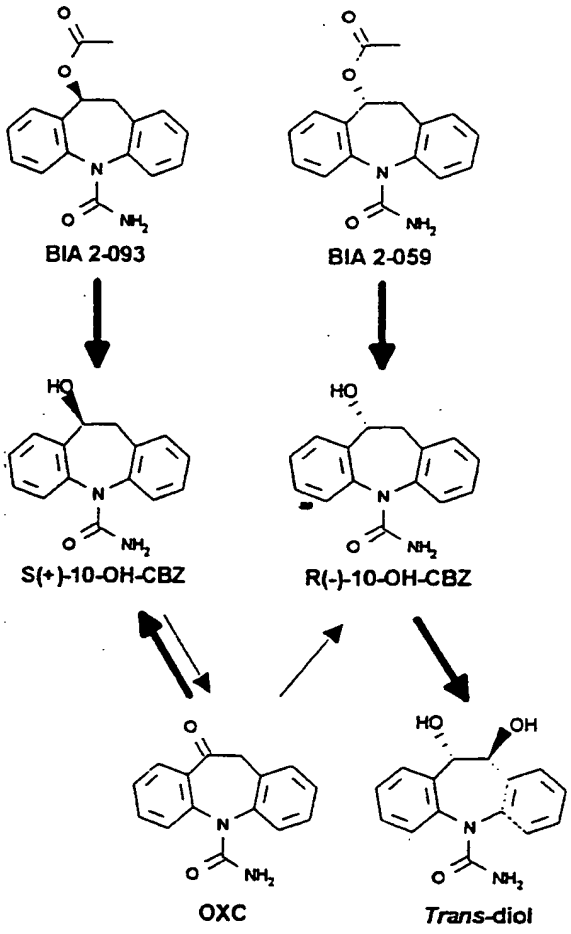

Fig. 5. Proposed metabolism of BIA 2-093 and BIA 2-059 in humans.

Since the reduction of OXC in the rat liver stereoselectively forms the *S*(+)-isomer, the enantiomeric purity of the active 10-OH-CBZ compound is successively lost after treatment with BIA 2-059 or *R*(−)-10-OH-CBZ, respectively. However, treating the animals with BIA 2-093 or *S*(+)-10-OH-CBZ leads to an enantiomerically pure metabolism. In mice, the same stereoselective behaviour could be found except for one difference. Mice cannot reduce OXC very effectively and, accordingly, hardly any enantiomeric dilution was observable after treatment with BIA 2-059 or *R*(−)-10-OH-CBZ.

Based on results of the in vitro assays, the further metabolism in humans after hydrolysis can be expected to be insignificant in the case of BIA 2-059, and its enantiomer BIA 2-093 will be oxidized to OXC in very small amounts. The following fast reduction back to the 10-hydroxy compound leads mainly to the *S*(+)-isomer, therefore resulting only in a negligible dilution of enantiomeric purity of the active compound. On the other hand, BIA 2-059 will more likely result in the slow formation of the inactive *trans*-diol and therefore loose its antiepileptic activity slightly faster than its isomer, making BIA 2-093 more suitable for the treatment of epilepsy. A summary of the proposed human metabolic transformations of BIA 2-093 and BIA 2-059 is shown in Fig. 5.

In conclusion, BIA 2-093 and BIA 2-059 appear to be preferable drugs over OXC since they most likely exhibit a 'cleaner' metabolism in humans. Pharmacodynamically, BIA 2-093 and BIA 2-059 have been shown quite similar (Benes et al., 1999), but from a therapeutic point of view BIA 2-059 would be less appropriate for the purpose of treating epileptic patients due to its propensity to undergo inactivation to the *trans*-diol.

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Treating Bipolar Disorder: Toward the Third Millennium

by Heather S. Hopkins and Alan J. Gelenberg, M.D.

(This is the first part of a series of articles discussing treatments for bipolar disorder—Ed.)

Although lithium is still the only drug approved by the U.S. Food and Drug Administration for both the treatment of acute mania and the maintenance treatment of bipolar disorder (BD), it is not efficacious for many people with BD, and its side effects are problematic for many others. The search for alternative treatments for the 20% to 40% of "classic" patients who do not respond adequately to lithium or cannot tolerate it continues. Even more, nonclassic patients (for example, rapid-cyclers, patients with mixed and dysphoric mania, and those with comorbid substance abuse) seem even less likely to respond adequately to lithium. Because a minority of patients with BD remain euthymic on lithium alone, adjunctive treatments are also being studied.

Divalproex (Depakote) and olanzapine (Zyprexa) are approved for the treatment of acute mania, but no trial has shown their efficacy in prophylaxis. Carbamazepine (Tegretol) continues to be employed for acute mania, bipolar depression and maintenance treatment, but rigorous studies have not produced consistent, positive results. Investigators are now looking at newer anticonvulsants, such as lamotrigine (Lamictal), gabapentin (Neurontin), topiramate (Topamax) and tiagabine (Gabitril).

In contrast with prescribing practices in many other countries, where doctors primarily use lithium, many doctors in the United States are prescribing these newer therapies to their patients before rigorous studies have proven their effectiveness.

Lithium

Many double-blind studies have shown lithium to be more efficacious than placebo in the long-term treatment of BD (Goodwin and Jamison, 1990). Some recent studies, however, have obtained less favorable results (Silverstone et al., 1998; Gershon and Soares, 1997; Moncrieff, 1995). To test the hypothesis that the effectiveness of lithium in BD has diminished over the past 30 years, Baldessarini and Tondo (2000) reviewed the medical literature from 1970 to 1996 and analyzed 360 patients with BD who had started maintenance lithium treatment during this time period. They found no indication that benefits from lithium treatment in BD have decreased and suggest that less favorable results with lithium may be due to the inclusion in clinical trials of more patients with atypical, treatment-unresponsive illness. Gitlin and Altshuler (1997) agreed that a change in the type of patients treated in clinical settings (including more patients with comorbid disorders), as well as problems with compliance, contribute to the disparity between results from controlled studies and naturalistic data. Schou (1993) cited "insufficient information, support, and supervision" as a cause of poor results with lithium, but Maj and colleagues (1998) found a high dropout rate (almost 30%)—despite efforts to optimize compliance—in 402 patients who started lithium prophylaxis at a lithium clinic.

Patients with a classical presentation of BD—clear-cut onset and recovery from episodes, and an absence of comorbid complications—appear to respond better to lithium treatment than do patients with complicating factors. Grof and colleagues studied "excellent responders" to lithium to identify determining characteristics (as cited in Friedrich, 1999). They found that these patients experienced full remissions between episodes and no loss of efficacy over time. In contrast to theories of discontinuation-induced refractoriness (Post et al., 1992), patients who discontinued lithium in this study experienced no loss of efficacy when they restarted treatment (Grof et al., as cited in Friedrich, 1999). Coryell and co-authors (1998) also found no

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Treating Bipolar Disorder

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evidence that discontinuing lithium caused a worse future response.

There may be two different groups of patients with BD: those who are responsive to lithium versus those who are more responsive to anticonvulsants or other agents (Goodwin and Ghaemi, 1998; Swann et al., 1997). A potential problem, however, is that anticonvulsants may not have the same ability to protect against suicide. Approximately 19% of patients with BD commit suicide (Goodwin and Jamison, 1990). There is about a sevenfold reduction in suicidal behavior with lithium treatment compared with no treatment (Baldessarini et al., 1999), and lithium may decrease the suicide rate in patients with mood disorders, even when it does not decrease the number of mood episodes.

Conceivably, lithium could be an antisuicide adjunct for patients with BD.

In a multicenter, controlled trial in Germany comparing lithium with carbamazepine over 2.5 years in 378 patients with bipolar or schizoaffective disorder, no patient taking lithium committed suicide. While taking carbamazepine, however, five patients attempted suicide and nine committed suicide (Thies-Flechtner et al., 1996). In two independent analyses, patients at high risk for suicide showed reduced suicide rates after taking lithium, whether their response to lithium in terms of episode prevention was good, fair or poor (Friedrich, 1999). Conceivably, lithium could be an antisuicide adjunct for patients with BD, even if they are stable on other medications.

Anticonvulsants

Divalproex has overtaken lithium in the United States as a treatment for bipolar disorder. In particular, it and other anticonvulsants are used alone or in conjunction with lithium and/or other agents in patients with dysphoric or mixed episodes, rapid cycling, neurologic histories or comorbid substance abuse.

Divalproex and carbamazepine. Divalproex has been shown to be efficacious for the treatment of acute mania and is approved by the U.S. Food and Drug Administration for this indication. The study by Bowden et al. (1994) found that patients with acute mania who had a history of poor response to lithium were more likely to improve with divalproex. Patients with multiple prior episodes also did better with divalproex than with lithium. A recent one-year study did not establish a statistically significant superiority of divalproex over placebo for maintenance therapy, but it did show a trend for a maintenance effect (Bowden et al., in press). Results from a small study suggest that adding divalproex to lithium for the continuation and maintenance treatment of patients with BD may enhance efficacy, although it also increases the risk of adverse reactions (Solomon et al., 1997). The combination of lithium and valproate led to increased serum lithium levels in one-third of patients in one case series (Sharma et al., 1993) and in laboratory rats, who also showed a decrease in plasma valproate levels (Vargas et al., 1996).

Carbamazepine is considered a second- or third-line treatment for acute mania or maintenance therapy, but conclusive evidence for its efficacy is lacking. Recent studies have continued to show that it may be effective in some patients but not as effective as lithium. In Germany, Greil and others (1997) found no statistically significant differences between lithium and carbamazepine on survival analyses regarding hospitalizations and recurrences. Carbamazepine-treated subjects, however, required significantly more comedication with antidepressants or neuroleptics, and more dropped out of treatment due to severe side effects.

In another study, patients were randomly assigned to one-year sequential treatment with carbamazepine, lithium and the combination (Denicoff et al., 1997b). Many of the subjects had a history of psychosis and/or rapid cycling. Patients had the same number of episodes during the carbamazepine year (seven manic, six depressive) as during the lithium year (four manic, nine depressive), but fewer during the year of combination treatment (three manic, four depressive). Patients from this study who did not respond to either lithium or carbamazepine were enrolled in another crossover study (Denicoff et al., 1997a). After one year, six of 18 had moderate to marked responses to lithium plus divalproex, and three of seven responded to therapy with lithium, divalproex and carbamazepine. In a small open trial of carbamazepine for bipolar patients in a depressive or mixed episode, 63% of patients were considered to have entered remission after three weeks of treatment (Dilsaver et al., 1996).

In a study of young women with epilepsy, 43% on valproate monotherapy and 50% of those taking valproate and carbamazepine had polycystic ovary (PCO) syndrome (Isojärvi et al., 1993). A cross-sectional pilot study failed to find an association between divalproex and PCO syndrome in women with BD, but did find high rates of menstrual disturbances in women taking both divalproex and lithium (Rasgon et al., 2000). Therefore, although data are lacking in young women taking this drug for mood stabilization, there is a possible risk for PCO and menstrual disturbances.

Gabapentin and lamotrigine. Open-label studies, case series and individual reports have indicated that gabapentin and lamotrigine may be efficacious in the treatment of BD and that they might be considered as alternatives for primary or adjunctive therapy when more established treatments are ineffective or poorly tolerated (Bennett et al., 1997; Fatemi et al., 1997; Fogelson and Sternbach, 1997). Gabapentin may be superior to divalproex and carbamazepine for anxiety and agitation, whereas lamotrigine may have more antidepressant potency.

In one double-blind study, lamotrigine monotherapy at both 50 mg and 200 mg was found to be significantly superior to placebo for bipolar depression (Calabrese et al., 1999). Bowden and others (1999) found significant improvement among both rapid-cycling and non-rapid-cycling treatment-resistant patients in both depressive and manic symptomatology in an open trial of lamotrigine as monotherapy or in combination with other drugs. Informal reports suggest lack of efficacy for gabapentin in rigorously designed trials. An analogous agent, pregabalin, may undergo study.

Topiramate. Topiramate was approved as an adjunctive antiepileptic treatment by the FDA in late 1996. As with gabapentin and lamotrigine, it has not been systematically studied as a treatment for bipolar disorder. A few reports suggest it may be efficacious as an adjunctive treatment for patients with BD unresponsive to more standard treatments, including patients with rapid cycling (Chengappa et al., 1999; Marcotte, 1998; Marcotte et al., 1998). Suppes et al. (1998) found that 35% of patients who were hypomanic or manic and 50% of patients who were depressed were much or very much improved after one month of adjunctive treatment with topiramate. Coadministration of carbamazepine or divalproex lowers topiramate serum levels and plasma levels of divalproex. The side effects of topiramate include dizziness, somnolence, psychomotor slowing, ataxia and—in contrast to most other antiseizure medications—weight loss. Conceivably, it could be an adjunct to the many other antimanic agents and mood stabilizers that increase weight.

Tiagabine. Because the anticonvulsant tiagabine has a mechanism of action similar to divalproex, as well as antikindling properties, it might be another treatment for acute mania. In one small open trial, however, it produced only mild improvement in a few patients (Grunze et al., 1999).

Conclusion

For patients with BD who do not respond to or cannot tolerate lithium, there are now many alternatives, although few have adequate scientific support of their benefit in a large number of patients, in long-term treatment and in medication combinations. It seems prudent at this stage to use an evidence-based approach, starting with the medications whose efficacy is best established by large, rigorously designed trials. Treatment needs to be tailored to the individual patient, based on personal and family history of response and characteristics of the illness. Polypharmacy may be the answer for many patients, and psychotherapy can help provide long-term stability. The multicenter, collaborative Systematic Enhancement Program for Bipolar Disorder (STEP-BD) project, sponsored by the National Institute for Mental Health, may help tease apart the current confusion among treatment options.

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Trying To Solve the Prescription Drug Abuse Equation

y Arline Kaplan

lany clinicians equate drug abuse with ocaine, marijuana or heroin. Yet, a ational survey reveals that some 3.9 illion people in the United States urrently use prescription-type sychotherapeutic drugs (most often pain lievers, tranquilizers or stimulants) for nmedical reasons, far surpassing the 2.1 illion people who use heroin, cocaine d/or crack cocaine (Substance Abuse id Mental Health Services lministration [SAMHSA], 2000).

Most addicts who prefer prescription igs come to them through medical ors, warned Sheila Blume, M.D., addic- n psychiatrist and former New York te Commissioner on Alcoholism.

"Now, they may get it from more than doctor, or they may supplement it by ei drugs, but the ones that I have ted...started by having these drugs scribed for some reason and then they an to abuse them," she said in an inter- w with *Psychiatric Times*.

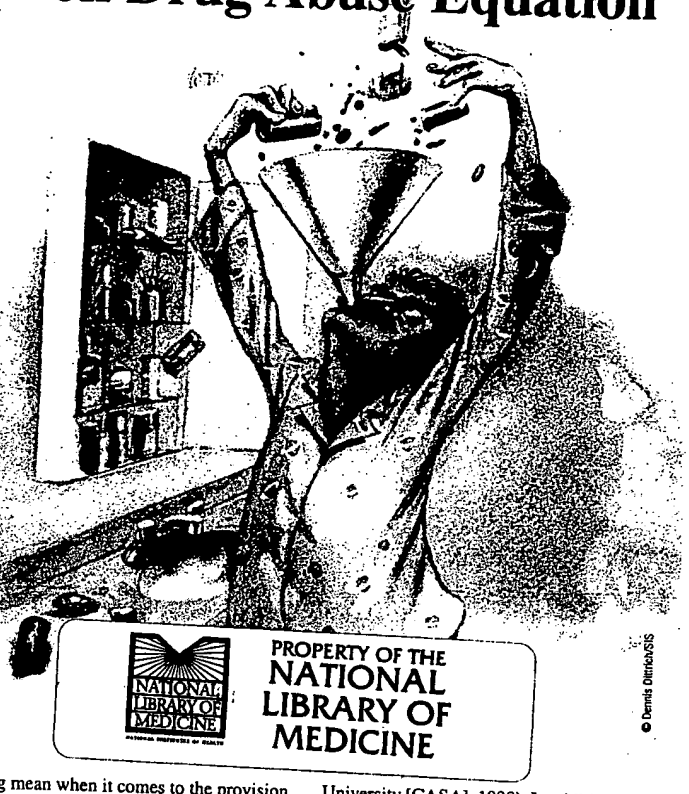
Health care providers need to be minded that the medications they scribe may have potential for abuse, she said, "and the more they hear it, the better."

The prevalence and incidence of illicit drug and alcohol use in the U.S. civilian population aged 12 and older is reported annually by SAMHSA in the National Household Survey on Drug Abuse (NHSDA). The 1999 results showed that 9.3 million individuals abused psychotherapeutics in the last year. The incidence of nonmedical prescription pain-reliever use rose significantly from the 1980s statistics of fewer than 500,000 initiates per year to 1.6 million initiates in 1998.

Looking at demographic factors, more youths aged 12 to 17 years (2.9%) and young adults aged 18 to 25 years (3.7%) abused psychotherapeutics than older adults (1.3%). More than half of current users were 26 years or older, and the rate for people aged 35 to 44 years was above 3%. Although generally more males than females abuse drugs, the rates are nearly equal with regard to psychotherapeutics (1.9% male; 1.7% female), the report authors said.

The Community Epidemiology Work Group (CEWG) survey, sponsored by the

(Please see Drug Abuse, page 3)



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mmentary

rugs, Crime and Race

obert L. DuPont, M.D.

onents of the nation's current poli- rohibiting use of drugs such as mari-, cocaine and heroin argue that such ies are racially biased against an-Americans and other minorities hat the drug war has failed. These isms were dramatically presented article "Criminalization of Drug by Joseph D. McNamara, D.P.A., in the September 2000 issue of *Psychiatric Times*.

My experience of over three decades of work in addiction medicine leads to quite different conclusions. While drugs and crime exist in all parts of the society, it is also true that problem-generating drug use and serious crime are indeed concentrated among the urban poor, some of whom are African-Americans. What does this disproportionate drug-related suffering mean when it comes to the provision of addiction treatment, law enforcement resources and other responses to the problems spawned by addiction? If the war on drugs has failed, has it failed disproportionately for the poor? Would drug legalization help the poor as some critics of current drug laws have proposed?

Examining the Data

It is well-documented that African-American non-Hispanics are significantly more likely than other groups to be incarcerated for both drug and non-drug offenses (National Center on Addiction and Substance Abuse at Columbia University [CASA], 1998). In addition to minority adults, the National Council on Crime and Delinquency (1999) found that African-American and Hispanic youths are treated more severely than white teenagers charged with comparable crimes at every step of the juvenile justice system.

When race/ethnicity is looked at by offense type, however, we find that the percentages by race were similar for drug law violations and violent and property crimes (the three major divisions of serious crimes). For example, African-American non-Hispanics made up 50% of state inmates serving sentences for

(Please see Crime and Race, page 8)

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Anticonvulsants in the Treatment of Bipolar Disorder

Paul E. Keck, Jr., M.D.
Susan L. McElroy, M.D.
Charles B. Nemeroff, M.D., Ph.D.

In the last decade, a proliferation of research has emerged concerning the use of somatic treatments with anticonvulsant properties, e.g., carbamazepine, valproate, clonazepam, oxcarbazepine, and electroconvulsive therapy (ECT), for patients with bipolar disorder. A sufficient number of controlled studies have been conducted to allow critical review of the evidence supporting the efficacy of these treatments for acute bipolar manic and depressive episodes, as well as for the prevention of subsequent episodes. Further research is needed to establish the prophylactic efficacy of anticonvulsants as maintenance therapies and, perhaps most importantly, to provide clinical and biological predictors of response.

(The Journal of Neuropsychiatry and Clinical Neurosciences 1992; 4:395–405)

In the last several years, a number of alternative somatic treatment approaches have been reported for patients with bipolar disorder who do not respond well to or who are intolerant of lithium treatment.[1] The development and testing of alternative treatments in controlled trials have been increasingly important because evidence has also accumulated over the past decade that a significant number of patients do not display an adequate acute[2] or prophylactic[3] response to lithium. One of the most active research areas has been the investigation of the clinical utility of anticonvulsant agents, particularly carbamazepine, valproate, oxcarbazepine, and clonazepam. Electroconvulsive therapy (ECT), a treatment with anticonvulsant effects, shares a longer history, augmented by more recent evidence, of efficacy in bipolar disorder. The body of evidence supporting the use of these newer pharmacologic agents is, however, uneven and incomplete, with much of the available literature consisting of studies that are uncontrolled and suffer other methodological flaws.

In the following review we critically evaluate studies of the use of these agents in the treatment of acute mania and depression and in the prevention of subsequent affective episodes. Because of the recent very large increase

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in the number of reports of treatment with these agents in bipolar disorder, we have restricted our analysis to double-blind controlled studies. We also briefly review the kindling model that has been proposed to explain the efficacy of these agents in bipolar disorder as well as to provide an animal model of the illness.

CARBAMAZEPINE

Until recently, carbamazepine was one of the few drugs investigated for its efficacy in psychiatry based on a theory derived from preclinical investigations. Departing from simple models of neurotransmitter depletion or excess, Post and Uhde[4] hypothesized that electrophysiologic abnormalities in the limbic system may provide a valid model of the pathogenesis of bipolar disorder. The limbic system has long been believed to play an integral role in the regulation of emotion.[5-7] Limbic structures are known to be particularly vulnerable to seizure induction by kindling when compared with most other brain regions.[8] Kindling is the phenomenon in which repeated application of subthreshold stimuli leads to overt seizures. In time, kindled rats exhibit spontaneous seizures. Synthesizing these observations, Post and Uhde[4] proposed that in vulnerable individuals, a series of stressors of sufficient magnitude may induce a reduced threshold for heightened electrophysiologic activity, producing the overt behavioral manifestations of a mood disorder. According to this model, medications effective in inhibiting the development of kindling should be effective in treating bipolar disorder. In early studies of anticonvulsant activity in amygdala-kindled seizures in the rat, carbamazepine emerged as a particularly effective agent.[9]

The notion that carbamazepine might exert therapeutic effects in mood disorders was also supported by the results of uncontrolled studies[10,11] in which mood elevation was noted in patients treated with the drug for epilepsy. However, these observations were limited, at the time, by the possible confounding influences of secondary improvement in mood resulting from better seizure control and/or the relief from possible behavioral toxicity from previous anticonvulsant regimens. Nonetheless, based on these preclinical and clinical findings, trials of carbamazepine in bipolar disorder were initiated. Interestingly, Okuma et al.[12] were pursuing similar studies in parallel in Japan, based in part on promising results from earlier uncontrolled trials.[13,14] As noted above, the use of carbamazepine in bipolar disorder now includes both uncontrolled and controlled studies; we have restricted our review almost exclusively to controlled trials.

Carbamazepine in Acute Mania

In at least 14 double-blind studies reported to date,[12,15-27] carbamazepine has been shown to be effective in the treatment of acute mania. These studies, summarized in Table 1, include comparisons of carbamazepine against placebo without concurrent psychotropic agents[15,16] (2 studies, $N = 19$); against placebo in combination with lithium[17] (1 study, $N = 5$); against placebo in combination with neuroleptics[18-20] (3 studies, $N = 40$); against lithium without concurrent psychotropics[21,22] (2 studies, $N = 76$); against lithium in combination with neuroleptics[23-25] (3 studies, $N = 145$); against neuroleptics without concurrent psychotropics[12,26] (2 studies, $N = 97$); and against neuroleptic in combination with neuroleptic[27] (1 study, $N = 17$). In part, this wide diversity in study designs attests to the difficulty in managing psychomotor agitation, severe insomnia, and other symptoms of mania in clinical trials without the use of adjunctive medications. In addition, many of these studies were performed without research funding, necessitating the use of more "naturalistic" designs. However, the administration of carbamazepine in combination with neuroleptics and/or lithium in a number of these studies[17-20,23-25,27] confounds interpretation of the findings because the improvement observed could not be attributed to carbamazepine alone. This is especially critical because the combination of carbamazepine and lithium has been reported to be synergistic in instances of poor response to either drug alone.[28-32] Similarly, the use of antipsychotic drugs in combination with carbamazepine in many studies[18-20,23-25,27] makes delineation of the contribution of carbamazepine to the therapeutic effect very difficult.

Six studies,[12,15,16,21,22,26] however, are unconfounded by concurrent lithium or neuroleptic administration and therefore allow for more meaningful interpretation. Pooled data from these studies reveal an overall response rate for carbamazepine in acute mania of 50%, compared with 56% for lithium monotherapy and 61% for neuroleptic monotherapy (differences not significant). Carbamazepine-treated patients showed significant improvement compared with placebo in the only placebo-controlled study[15,16] performed without concurrent lithium or neuroleptics.

In studies comparing carbamazepine with lithium,[21,22] both treatment groups improved significantly. However, Lerer et al.[21] found a trend toward greater improvement on the majority of Brief Psychiatric Rating Scale items for the lithium-treated group. Additionally, only 4 (29%) of 14 patients receiving carbamazepine were evaluated as having a good response compared with 11 (79%) of 14 patients receiving lithium. It is possible that with a larger sample size, differences in response rates that showed a trend toward a more favorable response for lithium

might have attained statistical significance. In the study by Small et al.,[22] a remarkable 29 (70%) of 43 acutely manic patients randomized to lithium or carbamazepine dropped out by 8 weeks of treatment because of lack of efficacy. At 8 weeks, 36% of carbamazepine-treated patients were rated as improved, compared with 37% of the lithium-treated patients. No significant differences emerged between the two drugs during the acute treatment period.

The efficacy of carbamazepine compared with chlorpromazine has been evaluated in two studies.[12,26] Okuma et al.[12] compared the two agents over a 6-week course in 60 patients with acute mania and reported a 70% overall rate of improvement for the carbamazepine group compared with 60% improvement in the chlorpromazine group. The incidence of side effects was significantly lower in the carbamazepine group. Grossi et al.[26] reported similar findings in a 3-week trial in 37 patients,

TABLE 1. Controlled studies of carbamazepine in acute mania

Study	*N*	Design	Concomitant Medications	Duration (Days)	Outcome
Placebo controlled					
Ballenger & Post,[15] Post et al.[16]	19	B-A-B-A CBZ vs. P	None	11 – 56	63% response on CBZ; significant relapse on placebo
Placebo + neuroleptic					
Klein et al.[18]	14	CBZ + HAL vs. P + HAL	HAL 15 – 45 mg/d	35	71% response CBZ + HAL; 54% response P + HAL
Müller & Stoll[19]	6	CBZ + HAL vs. P + HAL	HAL	21	Both groups improved, but CBZ + HAL improvement greater
Möller et al.[20]	11 CBZ 9 P	CBZ + HAL vs. P + HAL	HAL 24 mg/d Levomepromazine prn	21	No significant difference
Placebo + lithium					
Desai et al.[17]	5	CBZ + L vs. P + L	L; ND	28	CBZ + L response > P + L response by 14
Lithium controlled					
Lerer et al.[21]	14 CBZ 14 L	CBZ vs. L	None	28	79% response L > 29% response CBZ
Small et al.[22]	24 CBZ 24 L	CBZ vs. L	None	56	33% response rate both groups
Neuroleptic controlled					
Grossi et al.[26]	18 CBZ 19 CPZ	CBZ vs. CPZ	ND	21	67% response on CPZ; 59% response on CBZ
Okuma et al.[12]	32 CBZ 28 CPZ	CBZ vs. CPZ	None	21 – 35	66% response on CBZ; 54% response on CPZ
Neuroleptic + neuroleptic					
Brown et al.[27]	8 CBZ 9 HAL	CBZ + CPZ HAL + CPZ	CPZ	28	HAL group had higher dropout rate due to EPS
Lithium + neuroleptic					
Lusznat et al.[23]	22	CBZ + CPZ, HAL vs. L + CPZ, HAL	HAL, CPZ	42	No significant difference
Lenzi et al.[24]	22	CBZ + CPZ vs. L + CPZ	CPZ	19	73% response for both groups
Okuma et al.[25]	101	CBZ + Neuroleptics (80%) vs. L + Neuroleptics	Neuroleptics	28	62% response on CBZ; 59% response on mean level 0.46 mEq/l

Note: B-A-B-A = Placebo-Drug-Placebo-Drug; CBZ = carbamazepine; P = placebo; HAL = haloperidol; L = lithium; ND = not described; EPS = extrapyramidal side effects; CPZ = chlorpromazine.

with 10 (55%) of 18 carbamazepine-treated patients demonstrating moderate or marked improvement and 13 (68%) of 19 chlorpromazine patients responding. The authors noted that the onset of response appeared to be slightly more rapid in the carbamazepine-treated patients.

Four other studies[17-20] ostensibly compared carbamazepine with placebo, but in each of these studies patients in both treatment groups also received either lithium[17] or neuroleptics.[18-20] As noted above, concurrent treatment with these agents precludes attribution of therapeutic efficacy to carbamazepine. This is particularly confounded in the study by Klein et al.,[18] in which some patients received intramuscular haloperidol 30–80 mg at the beginning of the study, and in the study by Möller et al.,[20] in which patients received haloperidol 24 mg/d in addition to prn levomepromazine. In view of the antimanic effect of neuroleptics in these studies,[18-20] it is not surprising that differences between carbamazepine and placebo did not appear to be clinically meaningful.

Finally, four other studies[23-25,27] comparing carbamazepine with other antimanic agents—three with lithium, one with haloperidol—are also difficult to assess because adjunctive antipsychotic drugs were administered to all treatment groups. For example, in the study by Lusznat et al.,[23] the initial neuroleptic dose for patients receiving carbamazepine or lithium was 1,000 mg/d chlorpromazine equivalents.

Data bearing on predictors of response to treatment with carbamazepine are sparse. In an analysis of clinical characteristics associated with antimanic response to carbamazepine, Post et al.[33] found that patients who improved had more severe mania, were more dysphoric, and more frequently exhibited a recent history of rapid cycling; a negative family history of mood disorder was also associated with carbamazepine response.

In summary, although a number of controlled trials comparing carbamazepine with other agents in the treatment of acute mania are available in the literature, the number of studies that are not confounded by coadministration of antipsychotic drugs is limited to one placebo-controlled study[15,16] and two studies each comparing carbamazepine with lithium[21,22] or neuroleptics.[12,26]

Prophylaxis of Mood Disorder With Carbamazepine

Five controlled studies[23,34-37] have examined the efficacy of carbamazepine in the prevention of recurrent affective episodes in patients with bipolar disorder. These studies are summarized in Table 2. Okuma et al.,[34] in the only placebo-controlled study, reported a 60% response rate after carbamazepine treatment at 1-year follow-up compared with 22% on placebo. These findings closely parallel pooled outcome data from lithium prophylaxis studies showing mean relapse rates of 79% among placebo-treated patients compared with 37% for patients maintained on lithium.[53]

In four other controlled studies[23,35-37] carbamazepine has been compared with lithium as a prophylactic treatment. In each of these studies, concomitant administration of neuroleptics, hypnotics, and antidepressants was permitted for the emergence of manic and depressive episodes, respectively. A majority of patients required adjunctive treatment with these agents, although precise percentages are not provided. Thus, although four studies reported a favorable effect of carbamazepine in the reduction of affective episodes and a prolongation of euthymic intervals, this effect was incomplete for most patients. In fact, Murphy et al.[39] suggest that the methodologic limitations inherent in all of these studies leave the question of the prophylactic efficacy of carbamazepine unanswered. This is underscored by the findings of two recent naturalistic follow-up studies. In the first study, a retrospective survey of 55 patients (34 with bipolar disorder) treated with carbamazepine for 3–4 years, Frankenburg et al.[40] found that only 6 patients remained stable on carbamazepine monotherapy. Similarly, in a 4-year follow-up study of 24 patients with refractory affective disorders showing favorable acute responses to treatment with carbamazepine, Post et al.[41] found that one-half of patients followed after 4 years displayed a loss of prophylactic efficacy, a phenomenon that these investigators speculate may resemble the contingent tolerance to the anticonvulsant properties of carbamazepine in preclinical kindling models. In addition, the majority of this treatment-resistant cohort required maintenance treatment in combination with lithium and other pharmacologic regimens. Interestingly, Maj et al.[42] reported a similar waning of prophylactic efficacy over time for lithium. These investigators prospectively studied the 5-year outcome of lithium prophylaxis in 79 patients (43 bipolar, 36 unipolar) who reportedly showed an excellent response to 2 years of lithium treatment. Of 49 patients remaining on lithium, 14 (29%) relapsed; 4 of these patients had three or more episodes during the last 2 years of treatment after having been relapse free for 5 years. In this study, then, an escape from prophylactic efficacy was also demonstrated in a subgroup of patients despite continued treatment after initial early response.

Carbamazepine in Acute Depression

Two controlled studies[43,44] have evaluated the efficacy of carbamazepine in the treatment of patients with unipolar and bipolar depression. These studies are summarized in Table 3. Data from these studies indicate that, like lith-

ium, carbamazepine may have a less pronounced effect in the treatment of acute depression than of acute mania. In the first of these studies, Post et al.[43] reported marked improvement in 12 (34%) of 35 patients with treatment-resistant depression. A trend toward greater improvement in patients with bipolar compared with unipolar depression was observed, and the switch to placebo was associated with deterioration in carbamazepine responders. Although the finding of a 34% response rate is comparable with placebo response rates in parallel-design studies, this response rate is not insubstantial given the treatment-refractory nature of the cohort.

Small[44] described the results of an interim analysis of an ongoing study comparing the response of patients with treatment-resistant unipolar and bipolar depression with a 4-week trial of lithium, carbamazepine, or a combination of both drugs. All patients were then treated with both drugs for an additional 4 weeks. Groups randomized to carbamazepine and the combination displayed 32% moderate or marked improvement compared with 13% for lithium-treated patients. These results are consistent with those of Post et al.,[43] although the cohort studied by Small had significantly fewer bipolar patients.

From these studies, it appears that carbamazepine or carbamazepine in conjunction with lithium represent

TABLE 2. Controlled studies of carbamazepine and oxcarbazepine as preventative therapy in patients with bipolar disorder

Study	*N*	Design	Concomitant Medications	Duration (Years)	Outcome
Okuma et al.[34]	12 CBZ 10 P	CBZ vs. P	Not specified, but permitted for breakthrough episodes	1	40% relapse on CBZ; 78% relapse on P
Placidi et al.[35]	20 CBZ 16 L	CBZ vs. L	TCAs, CPZ, for breakthrough episodes	Up to 3	67% response rate for both groups
Watkins et al.[36]	19 CBZ 18 L	CBZ vs. L	Neuroleptics, antidepressants, for breakthrough episodes	1.5	Mean time in remission: CBZ 16 mos, L 9.4 mos
Lusznat et al.[23]	20 CBZ 21 L	CBZ vs. L	Neuroleptics, antidepressants, for breakthrough episodes	Up to 1	45% CBZ patients at 12 mos, 25% L patients at 12 mos; 25% CBZ rehospitalized, 50% L rehospitalized
Bellaire et al.[37]	46 CBZ 52 L	CBZ vs. L	ND	1	Mean reduction in number episodes comparable: 1.8/year to 0.67/year CBZ, 1.7/year to 0.7/year L
Cabrera et al.[49]	4 OX 6 L	OX vs. L	Neuroleptics (1 OX, 2 L)	Up to 22	3/4 OX, 6/6 L had significant decrease in affective episodes
Wildgrube[50]	8 OX 7 L	OX vs. L	ND	Up to 33	6/9 OX, 3/9 L treatment failures

Note: CBZ = carbamazepine; P = placebo; L = lithium; CPZ = chlorpromazine; OX = oxcarbazepine; ND = not described; TCAs = tricyclic antidepressants.

TABLE 3. Controlled studies of carbamazepine in acute depression

Study	*N*	Design	Concomitant Medications	Duration (Days)	Outcome
Post et al.[43]	24 bipolar 11 unipolar	B-A-B-A	None	Median 45	34% marked response CBZ; 54% response overall
Small[44]	4 bipolar 24 unipolar	L vs. CBZ vs. L + CBZ	None	28, then L + CBZ for 28	32% response CBZ, L + CBZ 13% response L

Note: B-A-B-A = Placebo-Drug-Placebo-Drug; CBZ = carbamazepine; L = lithium.

treatment alternatives for a subgroup of patients with treatment-resistant bipolar or unipolar depression. Controlled studies of carbamazepine in homogeneous, less treatment-refractory patients with unipolar depression and bipolar (types I and II) depression are necessary to clarify the efficacy of carbamazepine across the spectrum of patients with depression.

Oxcarbazepine in Acute Mania

A small body of preliminary data suggests that oxcarbazepine, the 10-keto analogue of carbamazepine, may also be effective in the treatment of mania.[19,45,46] Despite their structural similarity, these two agents have significantly different pharmacologic profiles. Unlike carbamazepine, oxcarbazepine does not appear to induce the hepatic oxidative enzyme system,[47] nor is it metabolized to an epoxide metabolite with sedating effects.[48] These differences suggest that oxcarbazepine may be an easier drug to administer, with fewer pharmacokinetic drug interactions, and easier to tolerate, with less psychomotor sedation.

The four controlled studies[19,45,46] that have assessed the efficacy of oxcarbazepine in acute mania are summarized in Table 4. At present, the optimal dosage range for antimanic efficacy of oxcarbazepine has not been established. For example, the average dosage of oxcarbazepine utilized in these studies ranged from 1,400 mg/d[46] to 2,400 mg/d.[46] In these trials, oxcarbazepine was superior to placebo[45] and comparable with haloperidol (15–20 mg/d;[19] 42 mg/d[46]) and lithium (1,100 mg/d, plasma

TABLE 4. Controlled studies of oxcarbazepine, valproate, and clonazepam in acute mania

Study	N	Design	Concomitant Medications	Duration (Days)	Outcome
Oxcarbazepine					
Emrich et al.[45]	6	A-B-A	None	Variable	4/6 (67% had > 50% decrease IMPS scores)
Müller & Stoll[19]	10 OX 10 HAL	OX vs. HAL	None	14	Mean decrease 55% BRMAS scores in both groups
Emrich[46]	19 OX 19 HAL	OX vs. HAL	HAL, L	14	Mean decrease 64% BRMS scores in both groups
Emrich[46]	28 OX 24 L	OX vs. L	HAL	14	Mean decrease 63% BRMS scores in both groups
Valproate					
Emrich et al.[52]	5	A-B-A	None	Variable	4/5 marked response; 1/5 no response
Brennan et al.[53]	8	A-B-A	None	14	6/8 marked response; 2/8 no response
Post et al.[54]	1	Crossover to P, CBZ, VPA, Phenytoin	None	Variable	Marked response to CBZ only
Pope et al.[55]	36	VPA vs. P	None	21	VPA > P on all scales
Freeman et al.[56]	27	VPA vs. L	None	21	92% response to L; 63% response to VPA
Clonazepam					
Chouinard et al.[66]	12	Crossover with L	HAL	10	CPM > L
Edwards et al.[67]	40	CPM vs. P	CPZ	5	CPM > P
Chouinard[68]	12	CPM vs. HAL	None	7	CPM, HAL comparable
Bradwejn et al.[69]	24	CPM vs. LPM	None	14	61% response to LPM; 18% response to CPM

Note: A-B-A = Drug-Placebo-Drug; IMPS = Inpatient Multidimensional Psychiatric Scale; BRMS = Bech-Rafaelson Mania Scale; OX = oxcarbazepine; HAL = haloperidol; L = lithium; P = placebo; CBZ = carbamazepine; VPA = valproate; CPM = clonazepam; LPM = lorazepam.

levels not described[46]) after 14 days of treatment. In general, oxcarbazepine was better tolerated than haloperidol and of comparable tolerability to lithium. Unfortunately, data from the two largest studies[46] are compromised by the use of haloperidol, and in some cases lithium, in both treatment groups. No studies, to our knowledge, have attempted to assess the efficacy of oxcarbazepine in the treatment of depression.

Carbazepine Preventive Treatment

Two preliminary controlled studies have reported on the prophylactic efficacy of oxcarbazepine in patients with bipolar disorder.[49,50] These studies are summarized in Table 2. Cabrera et al.[49] found significant decreases in the frequency of recurrent affective episodes in patients receiving oxcarbazepine or lithium. Interestingly, patients receiving oxcarbazepine in this study received only 900 mg/d, a dose significantly lower than those used in studies of acutely manic patients.[19,45,46] Wildgrube[50] found a higher rate of relapse (6/9) in patients maintained on oxcarbazepine compared with patients receiving lithium (3/9). However, the group receiving oxcarbazepine was significantly older and more severely ill at the initiation of treatment than the group randomized to lithium. The small sample size in each study also makes further interpretation of these data difficult. Clearly, larger studies are needed to establish the therapeutic efficacy and optimal dosage of oxcarbazepine as a preventive treatment.

VALPROATE

The first report of the efficacy of valproate in bipolar disorder appeared in France in 1966.[51] Since then, at least 16 uncontrolled studies have consistently suggested that valproate has acute and long-term mood-stabilizing effects in some bipolar patients, including those refractory to or intolerant of lithium therapy. More recently conducted controlled studies of valproate in acute mania have supported the findings from these uncontrolled reports. These studies are reviewed below.

Valproate in Acute Mania

Valproate has been shown to be effective in the treatment of acute mania in five controlled studies.[52–56] Summarized in Table 4, these studies include comparisons of valproate versus placebo in crossover trials without concurrent psychotropics[52–54] (3 studies, $N = 14$); against placebo in a parallel group trial using prn lorazepam as rescue medication[55] (1 study, $N = 36$); and against lithium in a parallel group trial using prn lorazepam as rescue medication[56] (1 study, $N = 27$).

In the only parallel-group, double-blind, placebo-controlled study,[55] 36 patients with bipolar disorder, manic phase (DSM-III-R), who were either lithium refractory or lithium intolerant, were randomized to valproate ($n = 17$) or to placebo ($n = 19$). Except for lorazepam (up to 4 mg per day for agitation or insomnia), no other psychotropics were permitted. Compared with the 19 placebo-treated patients, the 17 valproate-treated patients displayed statistically significant improvement on all three measures used: the Young Mania Rating Scale, an augmented version of the Brief Psychiatric Rating Scale, and the Global Assessment of Functioning Scale. Patients receiving valproate also required significantly less lorazepam. Further, in responders, the onset of antimanic response to valproate appeared rapid, with significant improvement evident within the first week of treatment.

In the only parallel-group, double-blind, controlled study comparing valproate with lithium in the treatment of acute mania (in which a placebo group was not employed),[56] lithium appeared more effective than valproate—perhaps because the response rate to lithium was usually high. Specifically, 12 (92%) of 13 lithium-treated patients improved, compared with 9 (64%) of 14 valproate-treated patients. However, this difference did not reach statistical significance by Fisher's exact test, two-tailed ($P = 0.20$).

Combining the results of these controlled studies, of 45 valproate-treated patients, 28 (62%) showed a moderate or marked reduction in acute manic symptoms, typically within 1 to 3 weeks. Preliminary evidence, largely uncontrolled, indicates that valproate may be synergistic with lithium, antipsychotic drugs, and carbamazepine in the treatment of some manic patients[57] and that certain predictors of antimanic response to valproate may exist. These may include rapid cycling (the occurrence of 4 or more mood episodes per year),[58,59] presence of substantial depression or dysphoria during mania (so-called dysphoric or mixed mania),[59] EEG abnormalities,[57] and a history of closed-head trauma prior to the onset of mood disorder.[60] In contrast, age, gender, duration of illness, presence of psychotic symptoms, presence of neurologic soft signs or subtle neurologic abnormalities, brain computed tomography findings, family history of mood or neurologic disorder, and response to other anticonvulsants were not associated with response to valproate.[57] A diagnosis of schizoaffective disorder, bipolar type, rather than bipolar disorder, however, was associated with a less favorable valproate response.[57] In the double-blind, placebo-controlled study of valproate performed at McLean Hospital,[55] shorter duration of illness was associated with a favorable valproate response, whereas history of rapid cycling and degree of depression or

dysphoria during mania was not.[61] However, the patient group was largely composed of treatment-resistant individuals.

Valproate in Major Depression and as Preventive Treatment

To date, there are no controlled studies of valproate in the treatment of acute unipolar or bipolar major depression, or in the long-term, prophylactic treatment of bipolar disorder. In three of four open studies,[59,62-64] valproate appeared more effective in the treatment of acute mania than of acute depression. Open studies, however, suggest that valproate may reduce the frequency and intensity of manic and depressive episodes over extended periods of time.[59] Further longitudinal data are sorely needed.

CLONAZEPAM

Clonazepam is a 7-nitrobenzodiazepin derivative anticonvulsant indicated for the treatment of myoclonic and absence epilepsy.[65] Four controlled studies,[66-69] summarized in Table 4, have evaluated the efficacy of clonazepam as an antimanic agent.

Two controlled trials,[66,67] one comparing clonazepam with lithium in a crossover design[67] and one parallel-group study comparing it with placebo,[67] found superior efficacy for clonazepam. However, in both studies antipsychotic drugs (haloperidol[66] and chlorpromazine[67]) were used in both treatment groups, significantly limiting the certainty with which response can be attributed to clonazepam. Chouinard[68] has also reported preliminary results of a 1-week double-blind parallel-group study of clonazepam versus haloperidol. The findings of this study, as described by the authors, suggest comparable efficacy for both drugs by 1 week of treatment. In a fourth study, Bradwejn et al.[69] compared the antimanic efficacy of clonazepam and lorazepam in a double-blind parallel 14-day study. Interestingly, patients who were randomized to lorazepam (mean daily dose at day 14, 13 mg) displayed significant improvement on seven measures of mania, whereas the clonazepam group (mean daily dose at day 14, 14 mg) failed to improve on any parameter. The authors hypothesized that the beneficial effects observed in the lorazepam group may have been due to its more rapid onset of action and greater bioavailability as compared with clonazepam.[69] In summary, it is important to note that all of these studies were confounded by small sample sizes, short durations of treatment, and difficulties in distinguishing putative specific antimanic effects from the nonspecific sedative effects of these drugs. Thus, although benzodiazepines may be useful in the tranquilization of the acutely agitated manic patient (where they may be used in place of or in conjunction with neuroleptics), it has not yet been clearly demonstrated that they have specific mood-stabilizing properties.

Clonazepam Preventive Treatment

The only controlled study of the efficacy of clonazepam in the prophylactic management of bipolar disorder examined clonazepam in combination with lithium. Sachs et al.[70] randomized bipolar patients requiring combined treatment with lithium and haloperidol to maintenance treatment with clonazepam and lithium or continued haloperidol and lithium. Analysis of the first 12 patients (6 receiving lithium and haloperidol, the other 6 receiving clonazepam and lithium) completing 12 weeks of treatment revealed no significant differences in rate of relapse between the two groups. However, 3 of 6 patients in the clonazepam group continued to require concomitant haloperidol, albeit at reduced dosages. These preliminary results, limited by the small sample size and use of antipsychotic in the clonazepam group, are of potential significance if borne out as the study progresses because they imply that clonazepam may be substituted for, or allow dosage reduction of, neuroleptics as an adjunct to lithium maintenance therapy. However, the only study that attempted to assess the efficacy of clonazepam alone as a maintenance treatment, Aronson et al.,[71] prematurely terminated the open trial after the first 5 bipolar patients enrolled relapsed within the first 2–15 weeks of treatment. The poor results observed in this study may have been attributable, in part, to the selection of lithium-refractory patients and rapid taper of neuroleptics after chronic administration before treatment with clonazepam.[72]

ELECTROCONVULSIVE THERAPY IN ACUTE MANIA

Electroconvulsive therapy (ECT) produces anticonvulsant effects and has also been shown to be an effective treatment for acute mania. Prospective randomized controlled trials of ECT have traditionally proved very difficult to carry out. In the only study of this type to date, Small and colleagues[73] randomized 34 patients with acute mania to ECT followed by maintenance lithium or to lithium for both acute and maintenance treatment. Patients receiving ECT showed greater improvement than lithium-treated patients after 8 weeks. Moreover, patients with dysphoric or severe mania showed a significantly better response to ECT than lithium. Indeed, the most significant predictor of outcome at 8 weeks was baseline ratings of depression. However, after 8 weeks of

treatment, there was no difference in response between the two groups. In addition, patients in the group receiving ECT were often switched to lithium by week 4, but not until week 6 did they show greater improvement than the group receiving lithium only. It is also possible that the group receiving lithium alone might have had a more robust response if higher lithium levels had been achieved. During the first 4 weeks of treatment the mean peak plasma level was 0.75 mEq/l. At 2-year follow-up, there were no significant differences in rates of relapse between the two groups. It is noteworthy that only bilateral ECT produced significant therapeutic effects.

Three other retrospective studies found ECT to be comparable in efficacy to antipsychotics[74,75] and lithium in the treatment of acute mania.[75] In one study,[76] patients treated with ECT were significantly more improved than patients treated with lithium, consistent with the results reported by Small and co-workers.[73]

To our knowledge, there are no controlled studies examining ECT as a maintenance treatment in patients with bipolar disorder, although case reports suggest that maintenance ECT may have prophylactic effects in some patients. However, two studies[77,78] of the impact of ECT on subsequent course of illness found that acute treatment of manic episodes with ECT was associated with greater rates of rehospitalization. In the first study of patients receiving ECT from 1940 through 1949,[77] the poorer outcome associated with ECT may have been due to a selection bias, with more severely ill patients receiving this treatment. In a similar study of a modern cohort, Winokur et al.[78] found that patients treated with ECT had more rehospitalizations (although no increase in the actual number of affective episodes) than manic patients who did not receive ECT. The authors interpreted this finding as consistent with greater motivation by a patient to consider rehospitalization and ECT because of a previous successful trial, or as a marker for a more aggressive treatment approach by a patient's physician, or as an effect of the treatment on the course of illness producing more severe subsequent episodes leading to rehospitalization. Indeed, in the study by Small et al.,[73] in which patients receiving ECT were subsequently placed on maintenance lithium, long-term outcome did not differ between these patients and those receiving acute and maintenance lithium treatment.

CONCLUSIONS

From data presented in this review, it is evident that carbamazepine, valproate, and ECT are effective treatments for a significant number of patients with acute mania. Data bearing on the efficacy of carbamazepine and valproate as antidepressant treatments and of all three as preventive treatments are more preliminary. However, whether benzodiazepines possess specific antimanic or mood-stabilizing properties in addition to their nonspecific sedative effects remains to be definitively shown.

Aside from the importance of these findings in providing alternatives to lithium for patients with bipolar disorder, a number of important clinical and theoretical questions remain unanswered. First, much work is required to identify reliable predictors of response to these agents. For example, although preliminary data suggest that certain clinical features, such as severity and dysphoria within the manic episode and rapid cycling, may predict a more favorable response to both carbamazepine and valproate,[33] response to one anticonvulsant is not necessarily predictive of response to another.[35,58] Similarly, dysphoric mania and rapid cycling have been associated with a more favorable response to valproate in some,[57,60] but not all,[62] studies. Interestingly, although one study[75] also found that degree of depression during mania at baseline predicted response to ECT, ECT has not been studied in rapid-cycling bipolar disorder, and thus whether or not rapid cycling predicts response to ECT is unknown.

Identifying biological predictors of response to these various modes of treatment is also important in elucidating their possible shared or differential therapeutic effects on proposed pathophysiologic mechanisms. Potential biological predictors of response such as MRI abnormalities, hypothalamic-pituitary-adrenal axis hyperactivity, and thyroid abnormalities are currently under study. That carbamazepine, valproate, and ECT share anticonvulsant and antimanic properties is an obvious but important starting point for the generation of hypotheses regarding their mechanism(s) of thymoleptic action. In particular, the study of new anticonvulsant agents with antikindling properties, as well as those with other mechanisms of action, in patients with bipolar disorder is one possible means of exploring the kindling model of the illness and of developing new treatments.

The last decade has witnessed the emergence of these anticonvulsants in the treatment of bipolar disorder. It is to be hoped that the next decade will provide an understanding of the mechanisms of action of these compounds and information concerning the neurochemical basis of this disabling disorder.

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